Develop New or Improved Approaches for Treating Disease and Disability

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Antibody Treatment Slows Progress of Diabetes

Background: Type 1 diabetes mellitus is a chronic autoimmune disease caused by the destruction of insulin-producing cells in the pancreas. Clinical studies have shown that treatment with immunomodulatory drugs, such as cyclosporine, slows the loss of insulin production. However, these drugs have toxic effects, such as impairing kidney function, and require continuous treatment. In mouse models of diabetes, brief treatment with a modified antibody was found to prevent or reverse diabetes for prolonged periods of time. The antibody is directed against CD3, a protein on the surface of immune cells called T lymphocytes that helps to activate the cells. A humanized version of the antibody, called hOKT3 -1(Ala-Ala), was developed for use in people.
Advance: At General Clinical Research Centers and other sites around the country, researchers investigated the effects of a 14-day course of treatment with hOKT3 -1(Ala-Ala) on the loss of insulin production in patients newly diagnosed with type 1 diabetes mellitus. After one year, 9 of the 12 antibody-treated patients had maintained or improved their insulin production, while only 2 of the 12 controls had a sustained positive response. Required insulin doses were also reduced in the antibody-treated group. No severe side effects occurred. Patients who had a response to antibody treatment showed an increase in the number of a T lymphocyte subset called CD8+ T cells, which may have immunoregulatory properties.

Implications: Treatment within the first six weeks after the onset of type 1 diabetes mellitus with a single course of anti-CD3 antibody arrested the deterioration of insulin production in the majority of patients for at least the first year of disease. The mechanism of antibody action is under investigation. he researchers speculate that antibody treatment may shift the immune system away from producing chemicals that participate in the autoimmune response against insulin-producing cells and toward the production of chemicals that protect these cells.

Herold KC, Hagopian W, Auger JA, et al: Anti-CD3 monoclonal antibody in new-onset type 1 diabetes mellitus. N Engl J Med 346(22): 1692-1698, 2002.

Beta-blockers Reverse Abnormal Gene Expression in Dilated Cardiomyopathy

Background: Certain nerves to the heart release the messenger chemical norepinephrine, which attaches to proteins called beta-adrenergic receptors on the heart surface and, among other functions, increases the contraction of the heart muscle, or myocardium. In dilated cardiomyopathy, one or both ventricles of the heart are impaired in their ability to pump blood and are also dilated. The condition is associated with a shift toward gene expression and thus protein production that is similar to that of a fetus rather than an adult. Treatment with a class of drugs called beta blockers, which prevent norepinephrine from binding to and activating beta-adrenergic receptors, improves ventricular function. To determine whether beta-blocker therapy also reverses the abnormal gene expression, specimens were collected from the myocardium of patients treated with either beta-blockers or placebo and tested for the expression of genes involved in heart contraction and pathologic overgrowth or hypertrophy of the myocardium.

Advance: Fifty-three patients with idiopathic dilated cardiomyopathy were randomly assigned to treatment with a beta-blocker (metoprolol or carvedilol) or placebo. After six months of treatment, 26 of 32 patients receiving beta blockers had an improvement in the ability of the left ventricle to pump blood. Responders also exhibited normalization of the expression of genes associated with heart contraction and myocardium hypertrophy. Expression of beta-adrenergic receptors was the same among those who responded to beta blockers versus those who did not.

Implications: In idiopathic dilated cardiomyopathy, functional improvement related to beta-blocker treatment is associated with changes in myocardial gene expression.

Lowes BD, Gilbert EM, Abraham WT, et al: Myocardial gene expression in dilated cardiomyopathy treated with beta-blocking agents. N Engl J Med 346(18): 1357-1365, 2002.

Potential New Treatment Preserves Insulin Production in Recent-Onset Type 1 Diabetics

Background: In type 1 diabetes, the patient's own immune system attacks and destroys the insulin-producing beta cells of the pancreas, leaving the patient unable to produce enough insulin to maintain normal blood sugar levels. Type 1 diabetes is also known as insulin-dependent diabetes because it forces a patient to depend upon daily, external insulin administration to stay alive. When first diagnosed with type 1 diabetes, patients' beta cells still produce some residual amount of insulin. Subsequently, however, most patients gradually lose more and more of their ability to produce insulin. The continued decrease in natural insulin production is thought to result from ongoing autoimmune destruction of the beta cells. In the past, researchers have been unable to intervene in the inexorable beta-cell destruction of this disease.

Advance: A recent small-scale clinical trial provides a glimmer of hope for those newly-diagnosed with type 1 diabetes. Twelve patients diagnosed within the previous six weeks were injected with a modified form of an antibody known as anti-CD3. This antibody works by suppressing the immune system's destructive T cells and by stimulating the production of protective immune-signaling molecules. Twelve other patients received no anti-CD3 injections and served as a control group. Nine of the 12 anti-CD3-treated patients maintained or improved their ability to produce their own insulin for one year following diagnosis. In contrast, all but two of the 12 untreated patients in the control group experienced a decline in insulin production.

Implications: Preservation of beta cell function is important because those patients with diabetes who can still make some insulin are able to achieve better control of blood sugar and have less risk of low blood sugar reactions than patients with little or no ability to produce insulin. This encouraging preliminary finding will now be tested in larger numbers of patients. If it proves effective in new-onset diabetes patients in larger trials, anti-CD3 treatment will then be studied in individuals at high risk for type 1 diabetes to determine whether it can actually prevent development of the disease.

Herold KC, Hagopian W, Auger JA, Poumian-Ruiz E, Taylor L, Donaldson D, Gitelman SE, Harlan DM, Xu D, Zivin RA, Bluestone JA: Anti-CD3 monoclonal antibody in new-onset type 1 diabetes mellitus. N Engl J Med 346(22): 1692-1698, 2002.

Trial of Combination Therapy for Treatment of Uncomplicated Malaria in Uganda

Background: Malaria currently kills about 3,000 people each day; 90 percent of these deaths occur in sub-Saharan Africa. Increasing malarial resistance to chloroquine, the long-time first-line drug in malaria treatment, in sub-Saharan Africa necessitates finding affordable alternative anti-malarial treatment. The combination of the antimalarial drugs sulfadoxine and pyrimethamine (SP) has been chosen to replace chloroquine as first-line therapy in several African countries. However, its use is limited by the rapid emergence of drug resistance. Another drug, amodiaquine, was widely used until 1990 when WHO withdrew endorsement of its use for malaria control programs based on reports of rare severe toxic effects. Although chemically related to chloroquine, previous studies suggest that amodiaquine remains effective even in areas with substantial chloroquine resistance. Therefore, the efficacy of amodiaquine-SP was compared to SP or amodiaquine alone in randomized trial in patients with uncomplicated malaria in Uganda.

Advance: The trial results demonstrate that amodiaquine-SP was more effective than SP or amodiaquine alone in curing malaria based on clinical symptoms and microscopic analysis of malaria parasites in blood smears. No severe adverse effects were recorded during the trial. In addition, fewer gametocytes, the parasite stage that infects mosquito vectors, were counted in patients given amodiaquine or amodiaquine-SP suggesting that treatment with this drug could reduce the transmission of malaria.

Implications: Both SP and amodiaquine are widely available in Uganda at a cost similar to chloroquine and much lower than other alternatives. Therefore, the treatment with a combination of SP and amodiaquine offers an effective, low cost anti-malarial therapy. Since the probability of the parasite developing resistance to two drugs with different biochemical targets is low and amodiaquine appears to inhibit the parasite stage carrying resistance mutations to mosquitoes, the amodiaquine-SP combination might delay the development of resistance to both drugs.

Staedke SG, Kamya MR, Dorsey G, Gasasira A, Ndeezi G, Charlebois ED, Rosenthal PJ: Amodiaquine, sulfadoxine/pyrimethamine, and combination therapy for treatment of uncomplicated falciparum malaria in Kampala, Uganda: a randomised trial. Lancet 358: 368-374, 2001.

Brief Intervention Leads to Long-Term Reduction in College Drinking

Background: Recent surveys have documented high rates of heavy drinking among college students. Heavy drinking by college students often leads to violence, date rape, accidents, and numerous other negative consequences. Few interventions have a documented positive impact in changing college student drinking behavior. In particular, commonly offered educational programs have little impact. However, brief, non-confrontational counseling sessions have shown promise as a means for reducing student drinking. Previous studies showed that a single brief counseling session greatly reduced alcohol-related problems among students at high risk for heavy drinking over a two-year period. In this study, researchers examined drinking patterns and related problems, and the effect of brief intervention, among a population of college students over a four-year period.

Advance: In this four-year follow-up, researchers found that the single brief intervention continued to yield significant benefits. High-risk students who had received the intervention continued to drink less alcohol and experience far fewer alcohol-related problems, compared with a control group of high-risk students that had not received the intervention. Alcohol consumption also declined in the control group, however, suggesting that much heavy drinking among college students is transitory, and that brief interventions can hasten declines in consumption.

Implications: The findings suggest that much heavy drinking among college students is transitory, and that brief interventions can hasten declines in consumption. The intervention's most significant preventive effect was in reduced negative consequences of drinking, a finding consistent with the goals of harm reduction interventions. Continued research will reveal the critical components for content and delivery of the brief intervention.

Baer JS, Kivlahan DR, Blume AW, McKnight P, Marlatt GA: Brief intervention for heavy-drinking college students: 4-year follow-up and natural history. Am J Public Health 91(8): 1310-1316, 2001.

Study Confirms Medication's Effectiveness in Alcoholism Recovery, Suggests Hormone Activation as Mechanism

Background: Scientists recently discovered that the drug naltrexone helps prevent relapse in detoxified alcoholics. One of the findings emerging from this research was that recovering alcoholics who do lapse into drinking again are less likely to drink heavily if they're on naltrexone.

In this study, scientists asked how naltrexone reduces the risk that alcohol-dependent people will drink heavily again after a period of abstinence. Among the issues scientists studied was craving for alcohol. Craving is more than a simple issue of desire versus will power; it's a potent physiological urge with biological underpinnings. It plays a central role in relapse among alcoholics. The investigators also examined the biological mechanisms through which naltrexone reduces heavy drinking. They already knew that naltrexone keeps components of the brain's opioid system from responding to certain substances, like some drugs, with the pleasurable sensations it usually evokes.

To explore these issues, investigators examined a group of 18 actively alcoholic men and women. For six days, half of them got naltrexone, while the remaining half got placebos. (Neither the participants nor the investigators knew which group got naltrexone or placebo during the study). All of the participants were allowed to drink at will during this time, but were required to be sober when they began testing on the last day. At that time, each of them got a priming drink, then were offered four drinks an hour for two hours. They had the option of taking each drink or pocketing its $3.00 cost. Throughout the study, investigators monitored patients' blood, not only for alcohol levels, but also for certain hormone levels. (Note: None of the participants were seeking treatment when recruited for this study. All were encouraged to undergo treatment and were offered treatment services at the end of the study.)

Advance: Alcoholics on naltrexone drank less alcohol, drank it more slowly, and reported less craving than did alcoholics on placebo. At the same time that participants on naltrexone reported less craving and drank less, their levels of cortisol and adrenocorticotropic hormones were higher than those of participants on placebo.

Implications: Naltrexone appears to reduce drinking by suppressing craving for alcohol. The increased hormone levels associated with naltrexone suggest that it might reduce craving by activation of a hormone system (the hypothalamo-pituitary-adrenocortical axis). This preliminary study suggests a promising avenue of research on the mechanisms through which medications like naltrexone exert their therapeutic effects.

O'Malley SS, Krishnan-Sarin S, Farren C, Sinha R, Kreek MJ: Naltrexone decreases craving and alcohol self-administration in alcohol-dependent subjects and activates the hypothalamo-pituitary-adrenocortical axis. Psychopharmacology 160: 19-29, 2002.

Addiction Medications Shown to Be Advantageous in Treating HIV Infection

Background: Medications to treat HIV infection have dramatically improved mortality rates among many patients with HIV. Because there are some individuals who do not respond adequately or who cannot tolerate some of the new medications and therapies, researchers are continuing to look for new ways to treat HIV infected patients. Many of those infected with HIV also suffer from addictive disorders, thus it is imperative that medications for addiction and HIV do not hinder the effects of one another. For example, researchers are looking at approved medications that are commonly used to treat alcoholism and opiate addiction, such as naltrexone, to ensure it does not affect the replication or transmission of the HIV virus as well as the actions of drugs used to combat HIV infection.

Advance: Using a cell culture preparation containing $CD4^+$ lymphocytes that were infected with HIV-1, researchers examined the effects of naltrexone and naloxone (another opiate antagonist) on HIV expression. The opiate antagonists were added to the cell culture alone and in combination with the antiretroviral drug zidovudine (AZT) and the protease inhibitor indinavir. Neither opiate antagonist had any effect of its own; however, both compounds markedly enhanced the effects of the antiviral agents on HIV-1 expression.

Implications: These data suggest that treatment of alcoholism or opiate dependence with naltrexone in patients who are also HIV+ is at least safe, and may, in fact, be therapeutically advantageous for both problems. Most importantly, these data suggest a novel strategy for enhancing the therapeutic actions of antiretroviral therapies, using a medication that has already been shown safe for use in humans. The mechanisms by which naltrexone potentiates the antiviral effects of AZT and indinavir require further study, but their identification could lead to new approaches to the treatment of HIV infection. Additionally, the results of the current study suggest that clinical trials may be warranted to evaluate whether naltrexone would be an effective adjunctive therapy for HIV+ patients who do not adequately respond to or who cannot tolerate high-dose treatment with current antiviral therapies.

Gekker G, Lokensgard JR, Peterson PK: Naltrexone potentiates anti-HIV-1 activity of antiretroviral drugs in $CD4^+$ lymphocyte cultures. Drug Alcohol Depend 64(3): 257-263, 2001.

Exposure to Drugs of Abuse Enhances Replication of the AIDS Virus

Background: Drug abuse is the single largest factor in the spread of HIV infection in the United States with half of all new HIV infections occurring among injecting drug users. HIV infection can cause a multitude of health problems, including brain damage and dysfunction. Research is now showing that many drugs of abuse can also damage the brain. Furthermore, some drugs of abuse may have detrimental effects on the immune system, thus allowing even greater impact of the AIDS virus. Since both HIV and certain drugs of abuse can cause damage to the brain, researchers are investigating whether abused drugs can potentiate damage to the brain that occurs with HIV infection.

Advance: In one study, scientists used a feline model to examine the impact of methamphetamine on the reproduction of feline immunodeficiency virus (FIV), a surrogate for HIV. They found that exposing brain cells that were infected with FIV to methamphetamine dramatically increased the cells ability to replicate FIV. The researchers exposed FIV infected astrocytes (a type of brain cell) to methamphetamine in concentrations equal to levels found in the bloodstream of adult methamphetamine abusers. They found that after two weeks exposure to methamphetamine, the FIV infected astrocytes increased their production of FIV by as much as 15 fold. Importantly, this increase occurred independent of any interaction with the immune system, indicating that infected brain cells may react differently or not at all to AIDS medications that act through the immune system. In another study, researchers used a hybrid human-mouse model to examine the impact of cocaine on HIV replication. They found that exposure to cocaine resulted in an acceleration of infection from HIV, as well as decreases in certain immune system cells.

Implications: Both HIV and certain abused drugs are known to cause damage to the brain. It has not been known, however, whether there is any interaction between abused drugs and the HIV virus that might increase health problems associated with either HIV infection or drug abuse. The present studies clearly indicate that certain drugs of abuse can potentiate infection from the AIDS virus. Furthermore, this potentiation was observed to occur in a type of brain cell, suggesting that abusing drugs may increase the progression of neuroAIDS. These results have important implications for prevention and treatment. HIV infection rates are high among drug abusers, with drug abuse being the largest factor in the spread of HIV. Sustained efforts are needed to educate drug abusers on the risks associated with drug abuse and other behaviors associated with the transmission of the AIDS virus. Furthermore, additional research is needed to better understand how drugs interact with the AIDS virus so that effective treatments can be developed to reverse any damage to the brain.

Roth M, Tashkin D, Choi R, Jamieson B, Zack J, Baldwin G: Cocaine Enhances Human Immunodeficiency Virus Replication in a Model of Severe Combined Immunodeficient Mice Implanted with Human Peripheral Blood Leukocytes. J of Infect Dis 185: 701-705, 2002.

Gavrilin M, Mathes L, Podell M: Methamphetamine Enhances Cell-Associated Feline Immunodeficiency Virus Replication in Astrocytes. J of Neurovirology 8(3); 240-249, 2002.

Molecular Mechanisms of Drug Tolerance: Implications for Improving the Treatment of Chronic Pain

Background: The last three decades have seen dramatic improvements in our understanding of what happens in the brain when someone is experiencing pain. This has led to the development of new medications and treatments for pain. Despite this, the most effective treatments for severe pain, which include opiate drugs such as morphine, are less than ideal. These drugs have side effects that can be undesirable and even life threatening. Furthermore, their use in chronic pain remains limited by the development of tolerance, a profound decrease in analgesic effect seen in most patients during prolonged administration of the opiate medications. Because morphine acts by attaching to a specific sites or receptors on neurons, known as mu receptors, considerable research efforts continue to focus on gaining a greater understanding of how mu receptors function as well as on how morphine impacts the mu receptors to produce analgesia and tolerance.

Advance: Researchers used a variety of approaches to characterize the changes in mu receptor function that occur during long-term exposure to morphine. They also examined whether some of these changes can be modified or prevented through the use of other compounds that bind to mu receptors. They found that long-term exposure to morphine reduced the endocytosis that normally occurs with mu receptors. Endocytosis is a process whereby receptors are taken into the interior of a cell. They also found that this reduction in endocytosis was associated with the occurrence of tolerance. When they combined morphine with [D-Ala2-MePhe4-Gly5-ol] enkephalin (DAMGO), a compound that also binds to the mu receptor, they found that endocytosis was increased. Furthermore, when they examined rats treated chronically with both drugs, they found that the increase in endocytosis was accompanied by a significant reduction in tolerance when compared to rats treated with only morphine. Thus, animals treated with both morphine and DAMGO did not require higher doses of morphine to maintain the same level of pain relief even after long-term administration.

Implications: These discoveries suggest exciting new possibilities for the treatment of chronic pain. The usefulness of morphine for the treatment chronic severe pain is limited by tolerance and the need to increase the dose of morphine to maintain long-term pain relief. DAMGO's ability to reduce the development of tolerance may have a dramatic impact on how chronic pain is treated. By reducing tolerance that occurs with long-term administration of morphine, patients with chronic pain will continue to experience effective pain relief at doses of morphine that are safe and effective. This will not only improve the quality of life for chronic pain sufferers, but it will reduce the occurrence of side effects and the possibility of misuse of or addiction to morphine.

He L, Fong J, Zastrow M, Whistler J: Regulation of Opioid Receptor Trafficking and Morphine Tolerance by Receptor Oligomerization. Cell 108: 271-282, 2002.

Incentive to Work Helps to Keep Addicts Drug Free: Proves Effective As Long-Term Treatment Approach

Background: Despite the chronic nature of drug addiction, most treatment programs approach addiction as an acute problem and offer only brief interventions. Last year, researchers reported on an experimental program that has been successful in helping drug-abusing women stay free of drugs by paying them a salary to attend a work/training program. In the Therapeutic Workplace, women in drug treatment are hired and paid to either perform assigned jobs or to participate in job training. To link salary to drug abstinence, patients are required to provide drug-free urine samples to gain daily access to the workplace. Program participation nearly doubled the patients' abstinence from opiates and cocaine, confirming the results of many years of previous research that demonstrate that reward-based treatment programs do result in decreased drug use. The researchers wanted to determine if long-term exposure to the program could extend abstinence over an extended period of time.

Advance: This study is continuation of a controlled study of 40 cocaine and opiate using women on methadone maintenance who were either pregnant or post-partum at the start of the study. The women were randomly assigned to either a Therapeutic Workplace or Usual Care Control Group. The critical features of the intervention include (a) hire and pay drug abuse patients to work in the Therapeutic Workplace, (b) promote drug abstinence by having routine drug testing to gain and maintain access to the workplace, and (c) use salary for work to reinforce drug abstinence. Results of this study, based on monthly urine drug samples, showed that three years after treatment entry, relative to the control group, participants in the Therapeutic Workplace were significantly less likely to be using cocaine (28 percent versus 54 percent) and opiates (27 percent versus 60 percent). Importantly, long-term exposure to the Therapeutic Workplace appeared to produce increases in abstinence from cocaine and heroin that were maintained for three years.

Implications: These findings show that requiring abstinence as demonstrated by a drug free urine test in order to gain access to work training and/or employment can effectively reduce drug use for up to three years in a very high-risk population with little education or employment experience. As such, it can serve as a long-term maintenance intervention for the treatment of cocaine and heroin addiction. The additional support provided by the Therapeutic Workplace serves as an alternative to existing welfare-to-work initiatives for women with dual drug use and unemployment.

Silverman K, Svikis D, Wong CJ, Stitzer ML, Bigelow GE: A reinforcement-based therapeutic workplace for the treatment of drug abuse: Three-year abstinence outcomes. Experimental and Clinical Psychopharmacology. (in press).

Contingency Management Behavioral Therapy Can Enhance Treatment for Opiate Addiction

Background: For opiate addiction there are several medications that have been developed and can be successfully used to treat addiction to heroin. Naltrexone, for example, blocks the subjective effects of heroin, is non-addicting and does not have strict regulatory requirements like methadone, allowing it to be delivered in a range of settings. However, for a variety of reasons including poor retention rates, naltrexone remains underutilized. A behavioral therapy called contingency management (CM), which provides vouchers redeemable for goods and services to individuals who remain drug free, has been shown in numerous studies to successfully treat cocaine-dependent populations in a variety of settings. Recognizing that the effects of pharmacotherapies are greatly enhanced when behavioral treatments are added, researchers wanted to determine if they could enhance naltrexone treatment by adding the CM behavioral therapy.

Advance: Fifty-five opioid-dependent individuals who have finished detoxification and were entering 12 weeks of treatment at a naltrexone maintenance program participated in this study. Participants were randomly assigned to one of the following: standard naltrexone maintenance; naltrexone maintenance plus low value conintgency management (CM); or naltrexone maintence plus high-value CM. This CM behavioral therapy provides vouchers redeemable for goods and services to those who achieve targeted behaviors, in this case drug-free urine specimens and thrice weekly ingestion of naltrexone. The participants could receive a maximum of $561.60 worth of items in the low CM; and a maximum value of $1,152 in the high value CM program if all 36 urine specimens were drug-free and the if the participant did not miss any naltrexone doses. Participants were assessed immediately before randomization, weekly during treatment, and at the end of the 12-week course of treatment. Follow-up was conducted at 1, 3 and 6 months after treatment. Twenty three participants completed the treatment, though almost all participants, including those who dropped out, were contacted as part of follow-up efforts. Participants randomized to either voucher condition remained in treatment longer than those assigned to just naltrexone treatment. They also took substantially more doses of naltrexone within treatment. There did not appear to be any significant difference in outcomes for those who could have received greater voucher values for their efforts, so magnitude of reinforcement did not seem to matter.

Implications: Results from this study are consistent with findings from other studies that show the promise of this behavioral therapy in improving retention, compliance and outcomes with naltrexone treatment and perhaps other pharmacotherapies. Capitalizing on behavioral approaches to enhance the efficacy of pharmacotherpy has important implications for improving outcomes among the large proportion of patients who are particularly compromised by compliance issues.

Carroll KM, Sinha R, Nich C, Babuscio T, Rounsaville BJ: "Continengy Management to Enhance Naltrexone Treatment of Opioid Dependence: A Randomized Clinical Trial of Reinforcement Magnitude." Experimental and Clinical Psychopharmacology 10(1): 54-63, 2002.

Behavioral Couples Therapy for Drug-Abusing Patients Reduces Partner Violence and Improves Children's Psychosocial Functioning

Background: Among the many devastating consequences of drug addiction and alcoholism are deleterious effects on the family environment and on the psychosocial development of children in substance abusing households. Children of parents with alcohol or drug problems are at risk for developing emotional, behavioral and social problems. Concurrently, evidence suggests that problems with alcohol and/or drugs are associated with a greater risk for intimate partner violence. Studies have shown that the prevalence of partner violence is more than two times higher among drug abusers than that observed in the general population. Although some studies have suggested that behavioral couples therapy may help reduce inter-partner violence and improve children's psychosocial functioning, no studies have rigorously examined this question.

Advance: In a series of studies, researchers administered Behavioral Couples Therapy (BCT) to drug-abusing men and their spouses. In one study, 80 couples were randomly assigned either to BCT or to an individual-based treatment (IBT). Although the couples in each treatment condition were equivalent on the level of partner violence before treatment, significantly fewer couples in the BCT reported partner violence in the year after treatment than did couples in IBT. This reduction in partner violence occurred even though violence reduction was not specifically addressed in the therapy.

In another study, 64 couples with children were randomly assigned to BCT, IBT, or to a couples-based psychoeducational treatment. While men in all three treatments showed significant improvements in abstinence from drugs immediately after treatment, men receiving BCT with their spouses maintained these improvements significantly longer than did men receiving the other treatments. Further, although the children of couples in the three treatments were equivalent on psychosocial functioning before treatment, children of couples receiving BCT showed significantly more improvement in emotional and behavioral problems than did children whose parents received the other treatments. These findings are of particular importance given that at pretreatment, approximately one third of children living with an alcohol-dependent father and one half of children living with a substance-abusing father exhibit emotional and behavioral problems consistent with psychosocial impairment.

Implications: These studies indicate that BCT can not only be effective for reducing drug abuse, but can also significantly reduce partner violence while also improving psychosocial functioning of children in these families. Thus, effective couples' treatment for substance abuse can have a lasting impact beyond the targeted substance abuse, leading to a better relationship between the couple and improvements for the children. These results support the addition of BCT in drug treatment programs.

Fals-Stewart W, Kashdan TB, O'Farrell TJ, Birchler GR: Behavioral Couples Therapy for Drug-Abusing Patients: Effects on Partner Violence. J of Substance Treatment 22: 87-96, 2002.

Kelley ML: Couples- Versus Individual-Based Therapy for Alcohol and Drug Abuse: Effects on Children's Psychosocial Functioning. J of Consulting and Clinical Psychology 70(2): 417-427, 2002.

The Side Effects of a Misspelling

Background: Many people are surprised to learn that medicines may only work properly in a subset of the people who take them. If a drug doesn't work properly, a person may experience side effects or no therapeutic effect at all. What's more, whether or not people develop side effects – and if they do, which ones they'll have – varies widely. While many factors such as diet and environment can help account for this variability in drug response, a key determinant is genes. A field of research called pharmacogenetics aims to unravel some of the biological reasons why people react so differently to medicines. Pharmacogenetics scientists have found many examples where a change in one or a few of the DNA "letters" that spell out genes can cause people to have different responses to medicines.

Advance: In a recent case, research physicians identified a group of cancer patients who develop a bad reaction to a chemotherapy drug called irinotecan, which is used to treat a variety of solid tumors. The scientists discovered that some patients have two extra letters in the gene that instructs the body to make a protein that metabolizes irinotecan and other drugs. Because of this tiny genetic difference, these people have less of the protein that breaks down irinotecan and thus have much higher levels of the medicine in their blood than most cancer patients given the same dose. When patients with the genetic misspelling took irinotecan, their white blood cell counts dropped dramatically, making them more likely to develop a potentially life-threatening infection. The same patients also experienced severe diarrhea, which can cause dangerous fluid loss in people who are already very sick.

Implications: Future genetic tests that screen for bad reactions to drugs such as irinotecan may help avoid toxic side effects and help determine the appropriate dose of chemotherapy drugs. Studies are under way to identify additional gene misspellings that could help physicians predict how patients will respond to irinotecan and other medicines.

Iyer L, Das S, Janisch L, Wen M, Ramírez J, Karrison T, Fleming GF, Vokes EE, Schilsky RL, Ratain MJ: *UGT1A1*28* Polymorphism as a Determinant of Irinotecan Disposition and Toxicity. Pharmacogenomics J 2: 43-47, 2002.

Cells' Sugary Coating Zaps Cancer

Background: Heparin is an inexpensive medicine that doctors use to "thin" blood and stop it from clotting. The medicine is widely prescribed to treat dozens of health conditions in which blood clotting can be especially dangerous, such as stroke and many heart disorders. Heparin and other complex sugar molecules like it cloak the surfaces of nearly all the cells in our bodies, as well as the surfaces of cancer cells. Recently, scientists have recognized the potential importance of a cell's sugar "coat" in the development of disease.

Advance: Researchers studying the biochemistry of heparin and other natural sugar molecules may have unearthed a brand-new potential use for heparin: treating cancer. To examine the possible role of heparin in cancer, biochemists injected an enzyme called heparinase into mice with tumors. Heparinase enzymes cut up complex sugars, generating molecules of heparin. These enzymes exist in several forms, each of which cuts complex sugar molecules in different places and generates different "trimmed" forms of heparin. The researchers found that injection of one particular heparinase treatment slowed the growth of skin, lung, and prostate tumors in the mice. Surprisingly, however, another member of this heparinase enzyme family actually sped tumor growth in mice. The scientists suspect that the sugary molecules interact with cancer-controlling proteins circulating in the blood and on the surfaces of other cells, and that slightly different forms of heparin can have very different effects on cell growth and cancer.

Implications: Further studies are needed to sort out the cancer-slowing and cancer-promoting properties of heparin. If the findings in experimental mice can be repeated in people, the appropriate form of heparin could potentially be put to use quickly as a cancer treatment, since it is already an FDA-approved medicine and as such has been demonstrated to be safe for human use. The results also illuminate a basic mechanism that may contribute to the development of diseases like cancer.

Liu D, Shriver Z, Venkataraman G, El Shabrawi Y, Sasisekharan R: Tumor Cell Surface Heparan Sulfate as Cryptic Promoters or Inhibitors of Tumor Growth and Metastasis. Proc Natl Acad Sci 99(2): 568-573, 2002.

Surprise Weapon to Treat Unwanted Angiogenesis

Background: Angiogenesis is the process in which existing blood vessels branch off to form new ones. The body controls angiogenesis very stringently, and it only occurs under limited circumstances, such as wound healing, pregnancy, and menstruation. Abnormal angiogenesis is involved in many health problems, including cancer and certain kinds of vision loss. Scientists know that many naturally occurring molecules control angiogenesis. There are no FDA-approved treatments to quell unwanted blood vessel growth, but angiogenesis-curbing molecules such as angiostatin and endostatin are currently in clinical testing for the treatment of cancer.

Advance: A team of biologists has unearthed a new and entirely unexpected potential therapy for abnormal angiogenesis. The researchers discovered a molecule called T2-TrpRS that can completely block angiogenesis in laboratory mice. Cells make T2-TrpRS by clipping it from its larger, "parent" form (TrpRS). The larger TrpRS protein has no impact on angiogenesis, but the shorter form regulates blood vessel growth.

Implications: The discovery of a novel, natural angiogenesis inhibitor showcases the value of untargeted basic research on cells and their proteins. The T2-TrpRS molecule may lead to new treatments for cancer and eye diseases caused by an overgrowth of vessels in the retina, such as a form of age-related macular degeneration and vision loss in people with diabetes.

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Otani A, Slike BM, Dorrell MI, Hood J, Kinder K, Ewalt KL, Cheresh D, Schimmel P, Friedlander M: A Fragment of Human TrpRS as a Potent Antagonist of Ocular Angiogenesis. Proc Natl Acad Sci 99(1): 178-183, 2002.

D-Cycloserine Enhances Extinction of Maladaptive Fear Responses

Background: In the 1990s, an NIH-funded investigator pioneered the use of an animal model for understanding the neural circuitry underlying fear conditioning. Fear conditioning occurs when a previously neutral stimulus (e.g., light) is paired with an aversive stimulus (e.g., foot-shock). After fear conditioning, the previously neutral, or conditioned stimulus (CS), presented alone, generates fear responses in the animal or human. In contrast, extinction is the process by which the association between the CS and the aversive stimulus is uncoupled through repeated presentations of the CS without the associated aversive stimulus. Over time, the fear response diminishes. Extinction training has been used as a treatment for patients who have developed maladaptive fear responses to particular stimuli or events. Much previous work has focused on discovering and investigating the brain regions involved in the fear conditioning circuit, including the amygdala, a brain region known to be involved in the processing and consolidation of emotionally significant events.

Advance: Neurons in the amygdala and other brain regions contain specific receptors that are known to be involved in learning. D-Cycloserine, a drug that binds to these receptors to enhance the activity of these cells, has previously been shown to facilitate learning in animals. This finding led to the hypothesis that D-Cycloserine might also facilitate the "unlearning" or extinction of previously learned associations. Using startle amplitude as a measure of fear conditioning and extinction, NIH-funded researchers conditioned animals to expect an aversive stimulus in the presence of a light. The animals were then given extinction training. Just prior to extinction training, half of the animals were given D-Cycloserine. The animals that received D-Cycloserine took significantly less time to extinguish the fear conditioned response than animals that did not receive the drug. D-Cycloserine without extinction training did not reduce the fear conditioned response. These results suggest that a combination of D-Cycloserine and behavioral training might be more effective in treating anxiety disorders than behavioral or pharmacological treatment alone.

Implications: A number of debilitating psychiatric disorders [phobias, anxiety, panic disorder and post-traumatic stress disorder (PTSD)] are characterized by the inability to inhibit maladaptive fear responses. The development of a drug that could enhance extinction learning would be of significant clinical benefit for persons suffering from these disorders. D-Cycloserine is already approved for the treatment of tuberculosis and has no significant side effects. Because the safety of this drug has already been established, this treatment could be developed fairly rapidly. The investigators are planning to begin clinical trials to determine the effect of this drug on extinction learning in humans. If successful, the combination of a behavioral approach – that is, extinction training – and pharmacological treatment would significantly accelerate the recovery from PTSD and other disorders marked by abnormal fear responses.

Walker DL, Ressler KJ, Lu K, Davis M: Facilitation of conditioned fear extinction by systemic administration or intra-amygdala infusions of d-Cycloserine as assessed with fear-potentiated startle in rats. J Neurosci 22(6): 2343-2351, 2002.

Work is an Important Component of Mental Health

Background: Reintegration into the workplace, and back into the family and the activities one was involved in before the illness is a priority issue for many people suffering from severe mental disorders. Rather than living a life that focuses mainly around their illness (e.g., medication visits, case management visits, trips to pick up disability payments, and attendance at day programs), they have voiced their preference for programs that allow them to work as a vital step to being more self-reliant. Congress has supported this perspective by passing legislation to eliminate work disincentives (Ticket to Work; Work Incentives Improvement Act 1999). However, most people with severe mental disorders living in community settings do not have jobs and vocational services are not included as part of their treatment plans.

A decade of research supports the idea that competitive employment in integrated settings for people with severe mental disorders is possible. One of the most successful models, Individual Placement and Support (IPS), developed at Dartmouth, emphasizes the importance of speedy rather than gradual reintegration into the work environment, with follow-along support given by mental health treatment teams. This model also has proven to be effective in New Hampshire for increasing rates of competitive employment and improving the worker's sense of well-being.

Advance: In this recent study, when IPS clients were compared with those receiving the state's usual psychosocial treatment program, there were few differences in the number and the length of time jobs were held during the two-year period, the hours worked and the compensation paid, and the time to secure the first job. However, the IPS group was far more likely than those in the standard training group to be employed (42 percent versus 11 percent) and to be employed competitively (27 percent versus 7 percent). The IPS employment model is more successful in getting people into the workforce. Now key issues must be addressed in helping those with severe mental disorders truly reintegrate into the community and find stability.

Implications: Vocational rehabilitation research for those with severe mental disorders now needs to concentrate on identifying the organizational, financial, and attitudinal barriers in the work environment that make sustained employment difficult. For example, the dynamics between the vocational support person and the client and IPS staff and employers need to be better understood. Examining all the factors – individual, dyadic, and organizational – that affect whether a person gets and retains a job will help to develop more effective models for community reintegration.

Lehman AF, Goldberg R, Dixon LB, McNary S, Postrado L, Hackman A, McDonnell K: Improving employment outcomes for persons with severe mental illnesses. Arch Gen Psychiatry 59(2): 165-172, 2002.

Behavioral Disturbances Related to Autism Helped by Meds

Background: Autism, a chronic mental disorder occurring in early childhood, is thought to be caused by abnormalities in brain development. Twin and family studies indicate a strong genetic contribution. It affects as many as 20 children per 10,000. Autism is characterized by symptoms of impaired social relatedness, delayed language, and restricted patterns of behavior. In addition, children with autism frequently exhibit serious behavior disturbances, such as self-injury, aggression, and tantrums in response to routine demands. Both behavior therapy and medications are used to treat these symptoms, but no study has determined which is most beneficial. Several different medications have been used to treat autism, but each has had limited success. To date, only haloperidol consistently has been shown to be superior to placebo for serious behavior problems. However, many clinicians have concerns about the neurological and other side effects with haloperidol so avoid its use in children. Atypical antipsychotics, such as risperidone, are medications that have been found to be effective for adults with psychosis, and have also potential therapeutic value for children with autism-associated severe behavioral disturbances.

Advance: At five clinical sites, 101 children with autism-associated severe behavioral disturbances, 82 boys and 19 girls, ranging in age from 5 to 17, were randomly assigned to receive either risperidone or placebo. The study found risperidone to be significantly more effective than placebo in improving behavior. Using a stringent definition of improvement, 69 percent of the children on risperidone showed major improvement by the end of the study, as compared with only 12 percent in the placebo group. This is the most positive improvement from medication observed in children with autism. Overall the medication was well tolerated with few neurological side effects, but there was substantial weight gain (an average of about 6 lb increase in the 8-week period).

Implications: A new drug has been found to help in decreasing the severe behavioral problems associated with autism. The new drug, risperidone, does not have the neurological side effects, but does cause weight gain, and needs to be studied further to determine its long-term effects and extended safety. The choice of which treatment to recommend to a particular child with autism must be individualized based on his/her specific needs.

RUPP Autism Network: A double-blind, placebo-controlled trial of risperidone in children with autism. N Engl J Med 347(5): 314-321, 2002.

Asthma Treatment

Background: Asthma ranks among the most common chronic conditions in the United States. Asthma causes breathing problems that must be promptly treated before they become life threatening. The disease disproportionately affects children, African Americans, and some Hispanics, especially those of Puerto Rican origin. Current research has provided important new information about treating this illness.

Advance: Low doses of inhaled corticosteroids (ICS) are used to treat asthma. Scientists have recently found that in some patients with persistent asthma whose symptoms are suboptimally controlled with a regularly scheduled ICS (triamcinolone acetonide) but whose asthma symptoms subsequently improve following the addition of a scheduled long-acting $ß_2$-agonist (salmeterol), the dosage of ICS can be reduced by up to 50 percent, but not eliminated, without a significant loss of asthma control.

Implications: This research provides enhanced treatment options for patients suffering from asthma.

Lemanske RF Jr, Sorkness CA, Mauger EA, Lazarus SC, Boushey HA, Fahy JV, Drazen JM, Chinchilli VM, Craig T, Fish JE, Ford JG, Israel E, Kraft M, Martin RJ, Nachman SA, Peters SP, Spahn JD, Szefler SJ: Inhaled Corticosteroid Reduction and Elimination in Patients with Persistent Asthma Receiving Salmeterol. JAMA 285 (20): 2594-2603, 2001.

Clinical Trial of a St. John's Wort Product Proves Ineffective

Background: Each year, 9.5 percent of the population, or about 18.8 million American adults, suffer from a depressive illness, ranging in severity from mild to life-threatening. In the year 2000, this resulted in over 10 million physician office visits. Both psychotherapy and a variety of medications have been demonstrated to be effective therapy for this condition. A popular herbal remedy for the treatment of depression, St. John's wort (*Hypericum perforatum*), has been used extensively in Europe and the United States; however, little is known about its effectiveness. A number of studies employing various St. John's wort products and patient populations have been conducted, however, results have been inconsistent, leaving the question of its potential for therapeutic benefit unresolved.

Advance: A randomized, double-blind, clinical trial compared one widely used St. John's wort product to placebo and sertraline, a prescription antidepressant drug, in the treatment of patients with well-defined major depression of moderate severity. It was the largest study of its kind, enrolling 340 adults, and long enough in duration to adequately assess whether the product could provide a meaningful therapeutic effect. Overall, the study's investigators found similar rates of response in patients taking the St. John's wort product and placebo according to primary and secondary measurement scales of depression. Although sertraline produced no greater effect than placebo on a primary clinical measure of depression, it fared better than placebo on a secondary measurement scale, yielding results consistent with its known benefits. The investigators concluded that the St. John's wort product employed in this study was not effective for the treatment of adults with major depression of moderate severity.

Implications: Additional studies, currently underway, should clarify whether other St. John's wort products have any therapeutic benefit for patients with less severe forms of this disease. To date, however, no studies of any St. John's wort product have demonstrated efficacy comparable or superior to conventional medications and psychotherapy. Thus, self-assessment and self-treatment for depression may pose public health risks and consequentially should be avoided. In contrast, licensed physicians are equipped to provide the best possible evaluation of, and treatment for, depression.

Hypericum Depression Trial Study Group: Effect of *Hypericum perforatum* (St. John's wort) in Major Depressive Disorder - A Randomized Controlled Trial. JAMA 287(14): 1807-1814, 2002.

Treatment of Drug Resistant Hairy-Cell Leukemia With Immunotoxin BL22

Background: Hairy cell leukemia (HCL) is a cancer of white blood cells called B lymphocytes. These cells look like they have hair projecting from the surface when viewed under a microscope. As the disease progresses, more leukemic lymphocytes accumulate in the bone marrow where white cells are made. The leukemic cells become so numerous they prevent the production of normal blood cells. The body then loses its ability to fight infection. B lymphocytes have a molecule called CD22 on their surface. Immunotoxins link a poison or toxin to an active molecule that guides the toxin into the interior of the cell, resulting in cell death. This type of treatment gets into the tumor faster while reducing the toxicity to the body since it only attacks a specific type of cell. BL22 is a recombinant (bioengineered) immunotoxin targeted to kill cells with CD22 on the surface.

Advance: Investigators tested BL22 in a Phase I clinical trial in HCL and other leukemia patients for whom standard chemotherapy had failed. In 11 of 16 patients, BL22 induced complete remission of the disease. These patients had no leukemic cells in their bone marrow or in their blood. Their spleens also returned to normal size. No other treatment has produced such a high rate of complete remission in chemotherapy-resistant HCL. Since the toxicity of BL22 treatment is low, multiple cycles of BL22 may be given to most patients. Two patients in the study had a serious reaction to BL22 – hemolytic-uremic syndrome, which involves a decrease in platelets and red blood cells and can lead to kidney failure. Both patients recovered completely and had complete remission of their disease. Following these two cases, investigators instituted precautionary measures prior to BL22 treatment to prevent this side effect, and no other cases of the reaction were reported.

Implications: Treatment with BL22 can induce complete remission of HCL. It may also kill malignant stem cells that develop into B lymphocytes, thereby eliminating the source of the disease. BL22 may also prove useful in treating other types of leukemia. Recombinant immunotoxins may also be developed for other types of cancer by targeting a key molecule on the cell surface.

Kreitman RJ, Wilson WH, Bergeron K, Raggio M, Stetler-Stevenson M, FitzGerald DJ, Pastan I: Efficacy of the anti-CD22 recombinant immunotoxin BL22 in chemotherapy-resistant hairy-cell leukemia. N Engl J Med 345(4): 241-247, 2001.

Brief Inactivation of *MYC* Oncogene Permanently Reverses Tumor Cell Production

Background: Cancer therapies designed to inactivate oncogenes (mutated normal genes that permit unregulated cell growth) might be expected to have serious toxicities because they also target critical pathways in normal cells. However, results from a recent study suggest that the brief inactivation of oncogenes during cancer treatment may lead to the sustained regression of tumors without inducing significant toxicity.

Advance: The investigators used a special genetic construct, the tetracycline regulatory system, with the *MYC* oncogene to conditionally turn on or off (activate or inactivate) the expression of the gene in a transgenic mouse model of *MYC*-induced malignant bone tumor, in which the genome was altered by the transfer of genes. The studies demonstrated that in the tumor-bearing mice, brief inactivation of *MYC* resulted in much slower tumor cell growth and the development of the bone cancer cells into mature bone. Surprisingly, subsequent re-expression of *MYC* not only failed to induce regrowth of the tumors, but actually produced cell death. Similar results were observed in laboratory tests using bone cancer cells.

Implications: The authors conclude that brief *MYC* inactivation permanently reverses the tumor-related characteristics of *MYC*-induced tumors, perhaps by causing changes in the tumor cells that disrupt the ability of *MYC* to sustain tumor cell production. Moreover, the tumor-related characteristics do not necessarily reappear upon reactivation of the oncogene. These results suggest that drugs that inactivate oncogenes intermittently and briefly may be effective, nontoxic cancer therapeutics.

Jain M, Arvanitiz C, Chu K, Daway W, Leonhardt E, Trinh M, Sundberg CD, Bishop JM, Felsher DW: Sustained loss of a neoplastic phenotype by brief inactivation of *MYC*. Science 297: 102-104, 2002.

Targeting Lymphatic Metastasis

Background: The major cause of death from cancer is spread of the primary tumor, which leads to the formation of new tumors (metastases) that are resistant to conventional chemotherapy. Malignancies spread through both blood and lymphatic vessels, but little is known about the role of the lymphatic system in metastasis formation. In a recent study, NIH-supported researchers investigated the lymphatic vessels associated with cancer in mice.

Advance: The researchers implanted cultured mouse tumor cells into the limbs of living mice. The experimental mice received tumor cells engineered to overexpress vascular endothelial growth factor-C (VEGF-C), a protein that stimulates the formation of lymphatic vessels. Compared to control mice, the experimental mice showed increases in lymphatic metastases. However, the experimental mice did not show increases in lung metastases, which typically are carried through blood vessels, not lymphatic vessels. Using imaging and other techniques that reveal lymphatic structure and function, these investigators showed for the first time that lymphatic vessels inside the tumor were not functional and therefore could not account for tumor cell spread to the lymph nodes. Rather, nodal metastases occurred only via lymphatic vessels located in the periphery of the tumors.

Implications: The findings suggest new cancer treatment strategies. This study shows that the expression of VEGF-C in experimental mouse tumors correlates with the incidence of lymph node, but not lung, metastasis. Since VEGF-C also plays a role in tumor formation, therapy directed at neutralizing VEGF-C at the tumor margins could potentially have the double effect of blocking metastasis by inhibiting the formation of both tumor-supporting blood vessels and lymphatic vessels.

Padera TP, Kadambi A, di Tomaso E, Carreira CM, Brown EB, Boucher Y, Choi NC, Mathisen D, Wain J, Mark EJ, Munn LL, Jain RK: Lymphatic metastasis in the absence of functional intratumor lymphatics. Science 296: 1883-1886, 2002.

Gershenwald JE, Fidler IJ: Targeting lymphatic metastasis. Science 296: 1811-1812, 2002.

Researchers Uncover Disparities in the Quality of Care for Colorectal and Prostate Cancer

Background: Although it is well known that some populations are less likely than others to receive the best available cancer therapies, researchers have not thoroughly studied whether this is true for colorectal cancer, where adjuvant therapy for surgery patients is the standard of care. However, certain groups (people age 75 or older, men, and African Americans) are more likely than others to die of this disease. Another source of cancer-related health disparities is the choice of hospitals and/or surgeons for cancer surgery. For many cancers, patient survival is higher when the surgery is conducted at hospitals and/or by surgeons that perform the operation frequently. Although this phenomenon has not been demonstrated with regard to survival of patients receiving surgery for prostate cancer, scientists have not examined whether choice of hospitals or surgeons might affect postoperative morbidity (e.g. urinary complications, incontinence, etc.).

Advance: NIH-supported researchers examined whether adjuvant therapy was used equally among colorectal cancer surgery patients of different ages, sex, and racial/ethnic backgrounds. They found that adjuvant therapy was used increasingly in all groups beginning after 1988, probably because of findings from large clinical trials confirming its effectiveness. However, some groups, particularly people over age 55 and African Americans, received adjuvant therapy less often than the overall patient population. When used, adjuvant therapy significantly reduced mortality in all groups. Another group of NIH-funded investigators discovered that men who underwent removal of the prostate at hospitals and by surgeons who performed a high volume of this surgery, experienced fewer postoperative and late urinary complications.

Implications: The discovery that standard therapy for colorectal cancer is less likely to be used in certain populations highlights a potentially serious shortfall in providing the best care to all people. Improved dissemination of adjuvant therapy might help reduce both the disparities and the overall mortality for this disease. The finding that rates of complications from prostate surgery depend on the experience of the hospital or surgeon with the procedure, suggest that more active education by professional societies might help optimize the quality of surgical care to patients.

Potosky AL, Harlan LC, Kaplan RS, Johnson KA, Lynch CF: Age, sex, and racial differences in the use of standard adjuvant therapy for colorectal cancer. Journal of Clinical Oncology 20(5): 1192-1202, 2002.

Begg CB, Riedel ER, Bach PB, Kattan MW, Schrag D, Warren JL, Scardino PT: Variations in morbidity after radical prostatectomy. N Engl J Med 346(15): 1138-1144, 2002.

FDA Approves Gleevec for the Treatment of Metastatic/Unresectable GIST

Background: Gleevec® is a novel anti-cancer drug targeted at the specific abnormality that causes the cancer. In chronic myelogenous leukemia (CML), Gleevec® turns off the signal for the protein BCR-ABL. Gleevec® was approved last year by the Food and Drug Administration (FDA) as an oral treatment for CML, a cancer of the bone marrow white blood cells. In 53 of 54 CML patients who were resistant to treatment with interferon, Gleevec® restored their blood counts to normal. This is a response rate rarely seen in cancer with a single agent. Fifty-one patients were still doing well after a year of treatment with only minor side effects. In a recent Phase III study of CML the independent data and safety monitoring board overseeing the trial recommended early disclosure of the data. Gleevec® was ten times more effective than standard interferon therapy in the trial.

The FDA granted accelerated approval this year for Gleevec® in treatment of patients with metastatic or unresectable (inoperable) gastrointestinal stromal tumors (GIST). Gleevec® blocks KIT, the molecular abnormality that causes uncontrolled growth of the cancer cells in GIST. This is the first molecularly targeted drug approved for treatment of GIST or any other type of sarcoma.

Advance: In a Phase II trial of the drug in GIST patients, 89 percent of patients showed marked clinical improvement. Fifty percent experienced tumor shrinkage, substantially higher than the rate achievable with standard chemotherapy (less than 5 percent). Since the results of this trial were so promising, NIH is sponsoring several additional studies of Gleevec® in GIST. The list of studies includes one intergroup Phase III trial in patients with metastatic/unresectable disease comparing a dose of 400 mg versus 800 mg daily. The results of this trial will be submitted by the drug manufacturer, Novartis, to the FDA as part of a Phase IV postmarketing commitment.

Implications: Gleevec® represents the new class of molecularly targeted drugs for cancer. The results with Gleevec® in CML and in GIST indicate that this targeted approach to treatment can work. Patients with GIST now have a promising advance in treatment with prospects for improved survival and less toxicity than with standard chemotherapy. Gleevec® may have other applications. It is being tested in glioma (a brain tumor) and soft tissue sarcoma. Researchers are studying other types of tumor cells to find specific cancer causing proteins. They will then be able to design Gleevec-like targeted treatments against those proteins.

Blanke CD, von Mehren M, Joensuu H, Roberts PJ, Eisenberg B, Heinrich M, Druker B, Tuveson D, Dimitrijevic S, Silberman SL, Demetri, GD: Efficacy and Safety of Imatinib Mesylate In Advanced Gastrointestinal Stromal Tumors. N Engl J Med 347(7): 472-480, 2002.

Patient-Specific Vaccines Help Fight Human B-Cell Cancers

Background: Most B-cell non-Hodgkin's lymphomas (NHL) are incurable and innovative treatments are needed. NIH-funded researchers have taken a variety of approaches to developing patient-specific vaccines against these cancers.

Treatment and prognosis of B-cell tumors varies widely, but the tumors have a common feature that makes them good candidates for developing patient-specific cancer vaccines. B lymphocytes express a unique cell surface protein called an immunoglobulin, with two variable regions that normally serve as recognition sites for foreign antigens. Immunogloblulins are capable of an immune response when coupled with a strong immunogenic compound called keyhole limpet hemocyanin (KLH) and given with an adjuvant. In this form they have been used to vaccinate patients who are in remission after chemotherapy. When these vaccinations trigger an immune response, patients have a superior clinical outcome. When a B cell undergoes malignant transformation, it creates a clonal population of cells, each of which expresses the same unique receptor, called an idiotype (Id). Anti-idiotypic antibodies can be produced that target the unique idiotype of each malignant clone. Dendritic cells are another element of the immune system whose main purpose is to capture and present exogenous (inhaled, ingested, injected) antigens to the immune system's T cells, which initiates an immune response. This unique antigen-presenting capability makes dendritic cells useful vehicles for delivering therapeutic cancer vaccines.

Advance: To determine whether B-cell lymphoma patients could mount an effective immune response following high-dose chemotherapy (HDCT) with autologous bone marrow transplantation (ABMT), the researchers tried two vaccination strategies. Patients were given either an Id vaccine alone, or a combination Id and dendritic cell vaccine. Both vaccines produced robust immune responses against KLH in nearly all patients. Vaccinations were consistently well tolerated. More than half (7 of 12) of the patients have experienced prolonged remissions ranging from 3 to more than 11 years post-chemotherapy.

Implications: These results document the ability of the recovering immune system to react against both self and non-self antigens and support the feasibility and safety of antigen-specific vaccination following HDCT/ABMT in patients with B-cell NHL.

Davis TA, Hsu FJ, Caspar DB, van Beckhoven A, Czerwinski DK, Liles TM, Taidi B, Benike CJ, Engleman EG, Levy R: Idiotype vaccination following ABMT can stimulate specific anti-idiotype immune responses in patients with B cell lymphoma. Biology of Blood and Marrow Transplantation 7: 517-522, 2001.

Molecular Profiles Identify Clinical Subsets of Patients

Background: Researchers and clinicians have been hampered in their efforts to distinguish differences in patients whose tumors appear to be alike. This difficulty has obscured the reasons why some patients respond to a given therapy while others do not, or why some tumors metastasize rapidly while others do not. NIH investigators are using comprehensive molecular analysis technologies to develop profiles of molecular changes in tumors that can predict clinical outcome. Such profiling based on gene expression is an adjunct to histologic and morphologic classifications of tumors.

Advance: Three separate groups of researchers using slightly different methods all found that gene expression profiling of lung tumors is a powerful tool in tumor diagnosis. The researchers found several subtypes of lung adenocarcinoma that differed in gene expression patterns and in clinical and pathological properties, including survival. The profiling can also help distinguish patients in stage I who are likely to be cured by surgery from those who require more aggressive treatment. Gene expression in lung cancer is also important since one of the key issues in lung cancer diagnosis is discriminating primary lung adenocarcinoma from distant metastases to the lung.

Similarly, other NIH-funded investigators were able to confirm the presence of three subtypes of disease in a group of locally advanced breast cancer patients, and differences in disease outcome were observed with each of the subgroups. Identifying subgroups of breast cancer patients will facilitate further clinical studies in which the response of these patients to specific therapies can be assessed. Another group of NIH-supported investigators, in collaboration with a large international consortium, the Lymphoma/Leukemia Molecular Profiling Project, identified three subgroups of diffuse large B-cell lymphoma (DLBCL) that had marked differences in outcome. In addition, these investigators identified a small group of genes associated with outcome that could be used to predict a patient's survival following chemotherapy. This predictor, distinct from the commonly used international prognostic index, may prove useful in the management of individual DCBCL patients.

Implications: These studies demonstrate that molecular profiling of tumors can be a powerful additional tool in identifying clinically important subsets of patients in at least three different tumor sites. The results will allow investigators to evaluate new interventions in patients who may not benefit from current therapies and may lead to the development of therapies targeting the molecular alterations present in these distinct subgroups of cancers.

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Rosenwald A, Wright G, Chan WC, Connors JM, Campo E, Fisher RI, Gascoyne RD, Muller-Hermelink HK, Smeland EB, Staudt LM: The use of molecular profiling to predict survival after chemotherapy for diffuse large-B-cell lymphoma. N Engl J Med 346(25): 1937-1947, 2002.

Scientists Find Ways to Overcome Resistance to Tamoxifen for Breast Cancer Treatment

Background: One type of breast cancer, known as "estrogen receptor positive" (ER positive), grows more aggressively in the presence of estrogen. The drug tamoxifen works well against this type of breast cancer by interfering with the body's production of estrogen. Unfortunately, this drug often works only for a time before the patient suffers a relapse. Researchers from NIH's Special Program of Research Excellence (SPORE) studied the molecular interactions between this drug and the cancer, examined why its effects don't last, and looked for treatment alternatives. These researchers also examined why in some women, but not others, high levels of a certain protein, HER-2, seemed to make ER positive breast cancers resist the effects of tamoxifen.

Advance: NIH SPORE researchers discovered that another drug, fluvestrant, which attacks the tumor through a somewhat different molecular mechanism, works against tumors that will not respond to tamoxifen. After several clinical trials, including one led by SPORE researchers, fluvestrant was approved by the United States Food and Drug Administration for treatment of breast cancers that are resistant to tamoxifen. These investigators also discovered that the protein HER-2, by itself, does not seem to make tumors resistant to tamoxifen. In their studies, only when the levels of two proteins, HER-2 and AIB1, were simultaneously elevated were tumors resistant to tamoxifen.

Implications: This research on the mechanisms of tamoxifen resistance is leading to new, effective treatment approaches. The recent findings on HER-2 and AIB1, if validated with further research, will open highly promising avenues for both diagnostic and therapeutic innovations.

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Needle Irrigation as a Treatment for Knee Osteoarthritis

Background: Knee osteoarthritis (OA) is a common and often disabling condition. Current medical therapies improve symptoms but they have not been demonstrated to modify the progression (worsening) of the disease process. Needle irrigation, primarily done by Rheumatologists, is the insertion of a needle into the arthritic joint followed by a flushing out of the joint with sterile water. It has been shown in previous studies to be superior to medical management, as effective as corticosteroid injection, and may be comparable to arthroscopic debridement (a formal surgical procedure performed by an Orthopaedic surgeon, where a viewing scope is placed into the joint, debris is removed, and the joint is flushed with larger amounts of water) except where there is a concomitant meniscal tear (the meniscus is a normal knee structure that is subject to injury and wear and tear). The results of these previous studies have been called into question because of deficiencies in study design and statistical power (i.e., a large enough number of patients to be sure that its conclusions are true).

Advance: NIH-supported researchers recently reported on the largest sham-controlled study of needle-irrigation for knee OA ever performed. 180 subjects with comparable knee OA were randomized to needle-irrigation or sham-irrigation (only the needle is inserted into the joint but there is no irrigation). Neither the patients nor the study personnel assessing their results were aware of which treatment they received. Subjects where followed for 12 months, and standard primary outcome measures were used. Results showed that there were no differences in the effects/results of true needle-irrigation versus sham-irrigation. Researchers concluded that the beneficial effects of needle-irrigation for knee OA appear to be due to a "placebo response" (i.e., the subjects report that they feel better just because they had something done). There were no major complications/adverse events reported in either group.

Implications: This study shows that needle-irrigation for knee OA is safe and feasible. Women rather than men, patients with more limited OA of the knee, and patients with a shorter duration of symptoms were found to have a more favorable response to treatment. The researchers were not able to support the use of needle-irrigation for the removal of small material/debris in the joint. These findings may be of use to patients and their health care providers regarding treatment options for the non-surgical management of knee OA.

Bradley JD, et al: Tidal Irrigation as Treatment for Knee Osteoarthritis. Arthritis & Rheumatism 46(1): 100-108, 2002.

New Insights into Bone-protecting Drug Action

Background: Drugs called bisphosphonates are the most commonly used agents for the prevention of bone loss. They initially attracted attention because of their ability to inhibit the action of osteoclasts, cells that dissolve, or resorb, bone. Controlled bone resorption is a normal part of bone remodeling, in which old or damaged bone is removed and replaced with new bone. However, net bone loss occurs in a variety of diseases, when bone resorption exceeds new bone formation. In some ways, bisphosphonates are more effective, in more situations, than might have been expected if they act simply to block bone resorption. For example, bisphosphonates seem to be surprisingly effective in alleviating the consequences of the "brittle bone disease" osteogenesis imperfecta, in which a genetic defect results in abnormal, easily fractured bone. Hints that bisphosphonates might have multiple effects first appeared several years ago when researchers showed that the drugs could reduce rates of cell death (called apoptosis) among osteocytes, a particularly crucial population of cells in bone. Osteocytes are cells that have become embedded in the bone as it forms. There is much evidence that osteocytes are responsible for sensing mechanical loading, and when bones are unloaded, as in prolonged inactivity or space flight, the rate of apoptosis among osteocytes increases. Recently, it has become clear that several other situations leading to bone loss also involve increased osteocyte apoptosis. It may be that preserving living osteocytes is as important a goal in drug development as blocking bone resorption. In fact, it may be that osteocyte apoptosis is actually one of the key events leading to the increased resorption that underlies bone loss.

Advance: Researchers have now shown that the antiapoptotic effect of a commonly used bisphosphonate is mediated by one of a group of proteins called connexins. Connexins are best known as the principal components of structures called gap junctions, which connect cells to other cells, allowing cell-to-cell communication. Gap junction connections are essential for many types of cells, including osteocytes. Surprisingly, however, the bisphosphonate effect is not dependent on gap junctions themselves. Instead, one particular connexin, called connexin43, seems to mediate the anti-apoptotic effect of the bisphosphonate independent of its role in gap junctions. This suggests that connexin43 has a previously unrecognized function in conveying "survival signals" to cells. There may be naturally occurring molecules that interact with connexin43 to prevent apoptosis.

Implications: The recognition that protecting osteocytes from apoptosis can prevent bone loss and fracture provides a new strategy for the search for more effective drugs. Beyond this, the identification of connexin43 as the mediator of the anti-apoptotic effect of bisphosphonates opens the door to understanding the molecular mechanisms by which apoptosis can be prevented. Isolating naturally occurring molecules that act through connexin43, or designing molecules specifically for such an interaction, may yield new drugs that protect osteocytes from apoptosis. The surprising effectiveness of bisphosphonates in treating osteogenesis imperfecta suggests that a wide range of bone diseases may respond to agents that preserve living osteocytes in bone.

Plotkin LI, Manolagas SC, Bellido T: Transduction of cell survival signals by connexin 43 hemichannels. J Biol Chem 277(10): 8648-8657, 2002.

A Strategy to Enhance the Effectiveness of Chemotherapeutics in Treating Brain Tumors

Background: Paclitaxel (Taxol) and its derivatives are chemotherapeutic agents that are used to effectively treat a variety of cancers. Because of their limited entry into the central nervous system, Paclitaxel (Taxol) and its derivatives are largely ineffective in treating brain tumors.

Advance: This study demonstrates that the primary barrier to Paclitaxel entry into the brain is a molecule called p-glycoprotein, which is a molecular pump at the blood-brain barrier that works to push foreign chemicals away from the brain. In mice given intravenous Paclitaxel, coadministration of a pump inhibitor compound substantially increases brain Paclitaxel levels and dramatically reduces the volume of implanted human brain cancer cells; without the p-glycoprotein inhibitor, Paclitaxel is ineffective.

Implication: This study identifies one mechanism responsible for the limited effectiveness of chemotherapeutics in treating malignant brain tumors and tests one strategy to overcome it. Since a wide range of drugs, including chemotherapeutics, HIV protease inhibitors, antivirals and antibiotics, are p-glycoprotein substrates and poorly penetrate into the brain, the strategy should have wide applicability. This study follows the development of confocal imaging-based techniques to identify mechanisms of xenobiotic transport at the blood-brain barrier.

Fellner S, Bauer B, Miller DS, Schaffrik M, Spruss T, Bernhardt G, Graeff C, Farber L, Gschaidmeier H, Buschauer A, Fricker G: Transport of Paclitaxel (Taxol) across the blood-brain barrier in vitro and in vivo. J Clin Invest 110(9): 1309-1318, 2002.

Fricker G, Nobmann S, Miller DS: Permeability of porcine blood brain barrier to somatostatin anlogs. Brit J Pharmacol 135: 1308-1314, 2002.

Miller DS, Graeff C, Droulle L, Fricker S, Fricker G: Xenobiotic efflux pumps in isolated fish brain capillaries. Am J Physiol 282: R191-R198, 2002.

Vitamins C and E Retard Fast-Developing Coronary Artery Disease Following Heart Transplantation

Background: Heart transplant patients tend to develop severe coronary artery disease (CAD) after transplantation; CAD is presently the most important condition limiting their long-term survival. Treatments to delay development and progression of CAD in transplant patients are urgently needed.

Advance: Recently published results of a clinical trial showed that supplementation with antioxidant vitamins C and E can retard the progression of CAD that follows heart transplantation. In the study, 40 patients who had undergone heart transplantation within the previous two years received either a combination of vitamin C and vitamin E or a placebo. After one year of treatment, measurements of arteriosclerosis (the hardening and thickening of the walls of the arteries) development were unchanged in the vitamin treatment group, but had increased significantly in the placebo group.

Implications: The results provide strong evidence that taking vitamins C and E could be a safe and inexpensive approach to increasing the survival and improving the quality of life of heart transplant patients.

Fang JC, Kinlay S, Beltrame J, Hikiti H, et al.: Effect of vitamins C and E on progression of transplant-associated arteriosclerosis: a randomised trial. Lancet 359: 1108-1113, 2002.

Treatment with Diuretics Especially Effective in Patients with a Specific Gene Variation

Background: Over 25 million Americans take medication for hypertension (high blood pressure). Responsiveness to medication varies greatly among patients, so it is often not clear which drug or drug combination should be used for a given patient.

Advance: Diuretics, drugs that increase the flow of urine to rid the body of extra fluid, are often prescribed to lower blood pressure. In a search for clues as to why some patients respond well to diuretics but others do not, investigators studying hypertensive patients looked at variants in the α-adducin gene, which is associated with renal sodium reabsorption and salt-sensitive hypertension. They found that patients with a particular form of the gene responded to diuretic therapy and had a lower risk of heart attack and stroke than patients with the same gene form who used other antihypertensive therapies.

Implications: These findings suggest that treatment with diuretics may be a very effective therapy for hypertensive patients who have a specific variation in the adducin gene. If findings such as these can be confirmed, clinicians may eventually start to screen hypertensive patients for selected genetic variants to determine the risks and benefits associated with treating them with various antihypertensive drugs. Such individualized treatment should not only reduce deaths but also be more cost-effective.

Psaty BM, Smith NL, Heckbert SR, et. al.: Diuretic therapy, the α-adducin gene variant, and the risk of myocardial infarction or stroke in persons with treated hypertension. JAMA 287(13): 1680-1689, 2002.

Inhaled Corticosteroid Standardization for Effective Asthma Management

Background: Inhaled corticosteroids (ICS) are the treatment of choice for lung inflammation associated with mild, moderate, or severe persistent asthma. The choice of a particular ICS is often based on convenience or cost factors. And though these drugs are widely used, no standardized method exists for comparing the beneficial and adverse effects of the many different ICS preparations and delivery systems available.

Advance: Researchers from the Asthma Clinical Research Network recently compared the different commercially available preparations of ICS and their delivery systems to assess their systemic effects and relative efficacy, and to find a benchmark by which to compare the various ICS and delivery combinations. Investigators determined that measuring the decrease in patient plasma cortisol levels was the most reliable method for evaluating the untoward effects of ICS. The cortisol levels produced in response to ICS treatment enabled a ranking of the ICS as to their systemic effects and the identification of doses of each of the different ICS preparations that resulted in equal amounts of cortisol in the plasma.

Implications: These standardization results will be useful in clinical trials as a means of comparing data from treatment with different ICS preparations. Results of this study should also help physicians prescribe for each patient the most effective dosage of ICS to manage the symptoms of persistent asthma.

Martin RJ, Szefler SJ, Chinchilli VM, et al.: Systemic effect comparison of six inhaled corticosteroid preparation. Am J Respir Crit Care Med 165: 1377-1383, 2002.

Gene Therapy Provides Long-Term Correction of Hemophilia B in Dog Model

Background: Hemophilia B is an inherited bleeding disorder resulting from a deficiency of factor IX, a protein that is essential for blood clotting. Current treatment, which entails regular intravenous infusion of clotting factor to prevent crippling and life-threatening bleeding complications, is costly and inconvenient, and carries a risk of transmission of blood-borne infections. The ultimate goal of hemophilia research is to offer a cure for the disease, and the strongest hope for a cure comes from gene therapy.

Advance: Researchers testing gene therapy cures in canine models of hemophilia B recently reported that they were able to introduce the factor IX gene to liver cells, which subsequently produced nearly enough factor IX to cure, not just treat, the disease. Moreover, production of therapeutic levels of factor IX was sustained for at least 17 months in three of four dogs, and the treatment did not seem to cause any liver damage.

Implications: The recent data continue to indicate that gene therapy for patients who have hemophilia B may someday become a reality. Moreover, the study provides important information that will be useful when designing human studies.

Mount JD, Herzog RW, Tillson DM, et al.: Sustained phenotypic correction of hemophilia B dogs with a factor IX null mutation by liver-directed gene therapy. Blood 99(8): 2670-2676, 2002.

Effects of Inspiratory Muscle Training on Patients with Severely Reduced Pulmonary Function

Background: Chronic obstructive pulmonary disease (COPD) affects an estimated 22 million Americans. About half of people with COPD are over 65. COPD is the nation's fourth leading cause of death and is estimated to be the third leading cause of death by 2020. $21.6 billion of direct costs annually is attributable to COPD. COPD affects breathing so severely in some patients that extremely severe shortness of breath stops even ordinary daily activities such as dressing and washing, as well as the ability to work, do household chores or participate in social activities.

Advance: Patients who had severe to very severe COPD were assigned to an inspiratory muscle training (IMT) group or to a group which received education about COPD and its treatment. Patients using the high-intensity inspiratory muscle training significantly improved inspiratory muscle strength, respiratory muscle endurance, and respiratory symptoms during daily activities and respiratory exertion. The patients showed that they could follow the training protocol and carry out the intensive training at home without supervision. This study also clarified some issues about how to measure both the endurance of respiratory muscles and difficulty in breathing.

Implications: Patients with COPD tend to accept the physical limitations imposed by the disease. This acceptance alters their perception of treatment success and they judge their health and quality of life by low standards. They also tend to underestimate the extent to which COPD can be managed. Successful management of COPD usually requires a complex plan of pharmacologic treatment and spacing activities with rest periods. The present study shows that inspiratory muscle training (IMT) can be a useful part of a treatment plan for those who have severely restricted lung function. The IMT treatment is able to be maintained by patients who otherwise cannot perform many daily activities without disabling shortness of breath. Quality of life is improved among patients who find it easier to breathe while doing activities of daily living. The IMT treatment also may reduce complications of serious pulmonary disease.

Covey MK, Larson JL, Wirtz SE, Berry JK, Pogue NJ, et al.: High-intensive Inspiratory Muscle Training in Patients with Chronic Obstructive Pulmonary Disease and Severely Reduced Function. Journal of Cardiopulmonary Rehabilitation 21: 231-240, 2001.

Structured Restorative Home Care Produces Better Health and Function After Acute Illness and/or Hospitalization in Older Persons

Background: Illness and hospitalization often initiate functional decline in older persons, and this decline can often persist long after the acute episode is over. An increasing number of older persons receive home care services after such episodes. The type of care and services that they receive during this period varies greatly, and may strongly affect the clinical course of their recovery and their functional abilities. However, little is known about the effects of specific home care strategies. Techniques to deal with various kinds of disabilities and health-related problems that are common among geriatric home care patients have been developed and, in some cases, shown to be effective in clinical trials. However, their applicability in home care has not been extensively studied.

Advance: A clinical trial in Connecticut tested the effects of a structured "restorative care" program on clinical and functional outcomes in 691 elderly home care patients compared to a matched group receiving the usual home care services in that area. The restorative care program consisted of the establishment of integrated teams of nurses, physical therapists, other therapists and home health aides for each patient. In addition to other health care, the teams applied structured interventions for disabilities, targeting risk factors that had been identified in previous studies. The interventions included exercises, behavioral changes, environmental adjustments and adaptive equipment, medication adjustments, and patient and family education.

Compared to the group receiving usual home care, significantly more participants on the restorative care program did not need rehospitalization or nursing home placement after the program was completed, and half as many had visits to emergency rooms during their home care. Functional abilities for living at home such as preparing meals, using transportation, shopping, doing laundry, and taking medicines appropriately were significantly better in the restorative care group, as was mobility. These effects occurred despite the fact the restorative care group received fewer home visits and the overall duration of home care was shorter than in the "usual care" group.

Implications: These results indicate that an integrated home care program targeting risk factors for disabilities can markedly improve the recovery and function of home care patients. However, the study was confined to one home care agency, and because home care populations and practices vary in different geographic areas, replication of these findings in other settings is needed before drawing conclusions about their general applicability. Further studies to determine how well specific components worked could lead to more refined strategies that might produce still better results.

Tinetti ME, Baker D, Gallo WT, Nanda A, Charpentier P, O'Leary J: Evaluation of restorative care vs usual care for older adults receiving an acute episode of home care. JAMA 287(16): 2098-2105, 2002.

Gene Therapy Repairs Brain Damage in an Animal Model of an Inherited Neurological Disease

Background: In lysosomal storage disorders (LSDs), infants inherit a faulty enzyme that is necessary for the normal breakdown of certain complex molecules. As a result, these molecules build up and progressively cause damage to the brain and other organs. Through years of painstaking work, scientists developed enzyme replacement therapies for some of the LSD's, such as Gaucher and Fabry disease, which successfully counteract some problems. However, the brain's normal protective mechanism, the blood-brain barrier, excludes enzymes and other large molecules from entering. Therefore, other therapeutic strategies are necessary to counteract the effects of LSDs on the brain.

Mucopolysaccharidosis type VII (MPS VII), or Sly syndrome, is a rare LSD that results from mutations in the enzyme beta-glucuronidase. The progressive accumulation of undegraded molecules, called glycosaminoglycans, in the brain leads to mental retardation and loss of hearing and vision, as well as causing problems elsewhere in the body, such as in the liver and joints. A mouse model of MPS VII mimics many aspects of the human disorder and has been essential for testing various therapeutic approaches, including gene therapy. A major unresolved question has been whether therapy begun after significant disease progression can restore brain function, rather than simply halting the process of accumulation.

Advance: Scientists have now shown that supplying a corrective gene to MPS VII mice not only halted progression of the disease, but produced dramatic recovery of impairments in learning and memory that had already occurred. The scientists spliced the necessary gene into a modified (and rendered harmless) version of the feline immunodeficiency virus, which carried the gene into brain cells. This type of virus was chosen because of its ability to infect brain cells. In addition to testing the mice on spatial memory tasks, the team assessed activity of genes associated with neuronal plasticity, that is, the ability of the brain to adapt. The results suggest that the effects of the gene therapy go beyond simply restoring normal enzyme activity and have other beneficial effects on the brain, which are now the focus of further investigation.

Implications: MPS VII is a rare disease, but these results may pave the way for treating more than 40 related LSDs and perhaps the many other enzyme deficiency disorders as well. Most importantly, these findings demonstrated recovery of neurological function after the disease had already progressed to a considerable extent. It is the first study to suggest that cognitive problems associated with a neurodegenerative disease might be reversible. Further investigations to understand how animals recover memory and other functions could point to new ways to treat many neurological disorders.

Brooks AI, et al: Functional correction of established central nervous system deficits in an animal model of lysosomal storage disease with feline immunodeficiency virus-based vectors. Proc Natl Acad Sci 99(9): 6216-6221, 2002.

Safe and Effective Treatment for a Rare Neurological Disorder

Background: Stiff person syndrome (STS) is a neurological disorder that causes disability and seriously affects quality of life; no satisfactory treatment is available. As suggested by the name, fluctuating muscle rigidity in the trunk and limbs characteristize STS, but people with this disorder also suffer muscle spasms triggered by heightened sensitivity to sensory stimuli, such as noise or touch, and to emotional distress. For these reasons, they are often unable to walk unaided or are afraid to leave the house because of frequent falls. STS is rarely diagnosed – perhaps in 1 per million persons – but some researchers believe the disorder is often misdiagnosed as Parkinson's disease, multiple sclerosis, fibromyalgia, psychosomatic illness, or anxiety disorder. Thus, the actual incidence may be much higher.

The cause of STS is not known. However, scientists have known for several years that people with STS have elevated antibodies to the enzyme glutamic acid decarboxylase (GAD). GAD is the enzyme that synthesizes gamma-aminobutyric acid (GABA) in nerve cells of the brain and spinal cord. GABA is the most common inhibitory neurotransmitter, that is, it tends to restrain the electrical activity of nerve cells, balancing the effects of excitatory neurotransmitters. So, diminished GABA might allow nerve cells that control muscle cells to be too active, resulting in stiffness or spasms.

Advance: A clinical trial has demonstrated that an immunologic therapy, intravenous immunoglobulin (IVIg), provides dramatic relief to people with STS. Following several preliminary studies of immune based therapies, the NINDS intramural research team conducted a double-blind, placebo-controlled clinical trial with 16 STS patients. Each person received three months of treatment with either IVIg or placebo, then switched to the other treatment. Neither the individuals with STS nor physicians evaluating the effects of the treatment knew who was receiving the active treatment or the placebo. Clinical measures of stiffness and of heightened sensitivity demonstrated the effectiveness of the IVIg. Furthermore, in contrast to the placebo group, six of the seven patients who received IVIg treatment first were able to walk more easily, or without assistance, for the first time in months. Their frequency of falls decreased, and they were able to carry out normal activities of daily living much more freely than before.

Implications: The findings demonstrate that IVIg is a safe and effective treatment for STS, a debilitating neurological disorder. The cause of STS and the mechanisms by which IVIg works are not well understood. Future research may reveal additional immune modulators. More generally, these results highlight the importance of immune-nervous system interactions in health and disease. Scientists have been studying many aspects of this interaction, from routine phenomena such as the fever response, to autoimmune diseases such as multiple sclerosis and myasthenia gravis, and immune reactions following spinal cord injury that may encourage or hinder recovery.

Dalakas M, et al: High-dose intravenous immune globulin for stiff-person syndrome. N Engl J Med 345(26):1870-1876, 2001.

Drug Treatment to Help Children with ADHD and Tics

Background: Attention deficit hyperactivity disorder (ADHD) and tics, including those associated with Tourette syndrome, are each common in children. Tic disorders and ADHD often occur together, perhaps reflecting the involvement in both disorders of a brain structure called the basal ganglia and its connections to the frontal lobes of the cerebral cortex. For decades, doctors who have treated children with ADHD and tics have been warned not to prescribe methylphenidate (Ritalin), the most common drug for ADHD, because of a concern that it could make the tics worse. However, there has not been sufficient information to reliably inform treatment decisions for these children.

Advance: The first randomized, placebo-controlled clinical trial of methylphenidate and another drug, clonidine (Catapres), in children with tics and ADHD has found that these drugs do not adversely affect tics. The study showed that each drug was individually helpful for treating ADHD in children with tics, and the two drugs affected different symptoms of ADHD. Methylphenidate improved attentiveness and helped children stay "on task," while clonidine helped control hyperactivity and impulsivity. The clinical trial also found that a combination of the drugs was more effective than either drug alone.

Implications: These findings provide needed guidance for treating children with tics and ADHD. While the study focused on children with both ADHD and tics, the differing effects of each drug alone suggest that clonidine may be an alternative to methylphenidate for children with ADHD who primarily have hyperactivity, while methylphenidate may be the better choice for treating inattention. The research team is planning further trials of other drugs, such as longer acting versions of methylphenidate and related drugs, and alternatives to clonidine which appear to cause less sedation.

The Tourette Syndrome Study Group. Treatment of ADHD in children with tics. Neurology 58: 527-536, 2002.

New Animal Model for Testing Therapeutic Approaches in Retinitis Pigmentosa

Background: Rhodopsin is the major intrinsic protein of photoreceptor membranes in the retina. Rhodopsin functions as a G protein-coupled receptor (GPCR) that is activated by light and initiates the phototransduction cascade in the rods, or dim light photoreceptors. Numerous mutations in rhodopsin have been associated with dominantly inherited blindness, such as the retinal degeneration called retinitis pigmentosa or RP. Rhodopsin mutations exhibit two different phenotypes. One is early-onset with a rapid and uniform loss of rod cells across the retina. The second has a slower course of vision loss, and degeneration spreads slowly from a disease focus in a single part of the retina. These naturally-occurring disease-causing mutations in rhodopsin have previously been identified only in humans. Thus, studies on the underlying mechanisms of retinal degenerations have focused on genetically engineered or mutagenized animals. These model systems have successfully demonstrated that both gene transfer and delivery of neurotrophic factors are successful therapeutic approaches to correct or lessen the impact of disease.

Advance: Progressive, naturally occurring hereditary retinal degenerations in dogs are widespread and have provided several models of human RP. Recently, an autosomal dominant form of retinal degeneration, in which a single copy of the mutant gene causes the disease, has been described in a dog model that closely resembles the human disease. The specific DNA mutation associated with this canine disease has been identified. Testing this animal's retinal function revealed that the disease was a progressive retinal degeneration from a single geographic locus. Additionally, defective dark adaptation in these dogs showed similarity to that seen in human patients with RP.

Implications: Slow progressive retinal degeneration is a major component of human autosomal dominant RP. Identification of a nonhuman rhodopsin mutant animal model offers opportunities for evaluation of the mechanisms involved in disease pathogenesis and of potential therapeutic approaches in humans with RP caused by rhodopsin mutations. This animal model will now permit studies of the effects of mutant gene dosage, adverse effects of environmental light, and benefits of supplemental nutrients. The temporal and functional progression of the disease in a canine model offers an ideal time window of opportunity for gene therapy. This mutant animal provides an invaluable tool to evaluate therapies before commencement of human clinical trials.

Kijas JW, Cideciyan AV, Aleman TS, Pianta MJ, Pearce-Kelling SE, Miller BJ, Jacobson SG, Aguirre GD, Acland, GM: Naturally occurring rhodopsin mutation in the dog causes retinal dysfunction and degeneration mimicking human dominant retinitis pigmentosa. Proc Nat Acad Sci 99(9): 6328-6333, 2002.

Bacteria Residing in Parasitic Worms Cause River Blindness

Background: Ocular onchocerciasis, commonly known as river blindness, occurs when a nematode worm infects the cornea. Although river blindness is rare in developed countries, it is the second leading infectious cause of blindness in the world. Over 18 million people are infected and approximately one million are visually impaired or blinded. The disease begins with repeated bites from black flies that transmit the nematode larvae. The larvae settle in the skin, where they grow to adulthood, reproduce, and then release millions of microfilariae that travel through the skin and can infect various eye tissues, including the cornea. When the microfilariae die, a massive inflammatory response is observed in the eye. This invasion of immune cells leads to corneal swelling, loss of transparency, and eventually blindness. Development and growth of a microfilaria depend on a bacterium, *Wolbachia*, which lives within the parasitic worm. Although treatment with anti-parasitic drugs kills the nematode directly, treatment of the infection with antibiotics kills the parasitic worm indirectly by attacking the bacteria.

Advance: Using a murine model of river blindness, the inflammatory response was examined in corneas subjected to extracts of worms that either were treated with doxycycline antibiotic, to kill the bacteria, or were untreated, and therefore contained living bacteria. When corneas were subjected to bacteria-free worm extracts (i.e. treated with antibiotic), no significant corneal haze or swelling was observed, indicating little or no inflammatory response. Alternatively, in corneas treated with extracts containing viable bacteria, neutrophils migrated into the cornea and a strong inflammatory response resulted in corneal clouding. This response required a toll-like receptor, TLR4, in the cornea that is sensitive to the bacteria. Mice lacking this receptor did not demonstrate a strong inflammatory response.

Implications: Treatment of river blindness with anti-parasitic drugs previously was considered effective, because it reduced the number of microfilariae. However, destruction of the worms leads to a blinding inflammatory response--not due to the worms, but to the bacteria residing within the microfilariae. Upon the death of the parasite, these bacteria are released into the corneal stroma and directly cause the inflammatory reaction that results in blindness. *Wolbachia* bacterium should be a good target for treatment, not only because it causes the death of the nematode, but also because it can reduce or eliminate the host inflammatory response caused by the bacterium. This could revolutionize treatment of river blindness, because the prompt destruction and removal of the *Wolbachia* bacteria should prevent the ensuing blindness associated with ocular onchocerciasis.

Saint Andre V,. Blackwell NM, Hall LR, Hoerauf A, Brattig NW, Volkmann L, Taylor MJ, Ford L, Hise AG, Lass JH, Diaconu E, Pearlman E: The role of endosymbiotic *Wolbachia* bacteria in the pathogenesis of river blindness. Science 295: 1892-1895, 2002

High Oxygen Permeability Extended Wear Contact Lenses Reduce Corneal Complications

Background: Light enters the eye through the transparent cornea that consists of multiple living cell layers and is bathed on the outer surface by the tear film. Since the cornea contains no blood vessels, its cells receive oxygen primarily by diffusion from the tear film, which is exposed to ambient oxygen levels in the air. Prolonged wear of rigid contact lenses is associated with development of various corneal complications, some of which can cause permanent visual impairment. Some of the more serious contact lens-associated complications, such as infection and inflammation, are caused by reduced corneal oxygen (corneal hypoxia) that develops during extended, overnight wear (EW) of rigid lenses. While previous studies had suggested that corneal hypoxia is the primary mechanism for such complications, no clear links between hypoxia and the incidence of complications have yet been identified. This uncertainty about the exact relationship between corneal hypoxia and adverse ocular complications associated with EW lenses has been explored in a controlled clinical trial of EW rigid lenses with different oxygen permeabilities. The study hypothesized that higher oxygen permeability lenses should lead to increased levels of available oxygen in the tear film, while lenses with lower oxygen permeability would lead to hypoxic conditions for the cornea.

Advance: Two hundred individuals were gradually adapted to wear EW rigid contact lenses. After this adaptation period, the subjects were wearing the EW lenses all day and night for 6 days per week, and they continued wearing the lenses for a month before the study began. Then, half the subjects were randomly assigned to wear EW rigid lenses with medium levels of oxygen permeability, and half were assigned to wear lenses with high permeability, i.e., twice that of medium group. The goal was for subjects to wear the lenses all day and night for 6 days per week for a period of 12 months. Although some subjects in both groups did not complete the one-year trial, those wearing medium oxygen permeability EW lenses lost three times the number of participants due to lens related complications. Also, it was observed that an increased level of corneal hypoxia resulting from the use of medium oxygen permeability lenses caused swelling of the cornea and compromised function.

Implications: The use of overnight, extended wear contact lenses is compromised by hypoxic conditions. Contact lenses with the highest available oxygen permeability should be used to maintain a healthy cornea.

Fusaro, RE, Polse, KA, Graham AD, Gan CM, Rivera RK, Lin MC, Sanders TL, McNamara NA, Chan JS: The Berkeley Contact Lens Extended Wear Study: Part I - Study Design. Ophthalmology 108(8): 1381-1388, 2001.

Polse KA, Fusaro RE, Graham AD, Gan CM, Rivera RK, Lin MC, Sanders TL, McNamara NA, Chan JS: The Berkeley Contact Lens Extended Wear Study: Part II - Clinical Results. Ophthalmology 108(8): 1389-1399, 2001.

Lin MC, Graham AD, Fusaro RE, Polse KA.: Impact of Rigid Gas-Permeable Contact Lens Extended Wear on Corneal Epithelial Barrier Function. Investigative Ophthalmology & Vision Science 43(4): 1019-1024, 2002.

Potential Therapy for Autoimmune and Allergic Diseases

Background: Immune cells known as T helper type 1 (Th1) or type 2 (Th2) play important roles in defending the body against pathogens by producing different types of secreted proteins known as cytokines. Th1 cells protect against intracellular pathogens such as bacteria by secreting large amounts of the cytokines interferon gamma (IFNγ) and tumor necrosis factor alpha (TNFa). In contrast, Th2 cells that are needed to control infections caused by extracellular parasites such as flatworms and roundworms secrete copious amounts of the cytokines, IL-4, IL-5 and IL-13. Cytokines function by instructing the cells of the body when to begin or stop growing, when to multiply, how long to live, and when to die. Although cytokines are important for many biochemical processes and are clearly beneficial in controlling diseases ranging from cancer to a variety of infectious diseases, their excessive production can be detrimental to normal cells. For example, persistent secretion of these cytokines is the cause of allergy and autoimmune diseases such as uveitis, multiple sclerosis, arthritis, and diabetes. Considerable evidence now indicates that the immune response of individuals that develop autoimmune diseases is dominated by Th1 cells that produce IFNγ while predisposition to allergic diseases is associated with elevated levels of Th2 cells and Th2 cytokines. A desired clinical outcome for these patients is to control the level of production of the toxic cytokines that cause autoimmune or allergic diseases.

Advance: Given the importance of maintaining appropriate levels of cytokines in normal cells, it is therefore not surprising that cytokine activities are themselves under stringent control. Scientists have identified a new family of proteins called suppressors of cytokine signaling (SOCS) in T cells. These proteins are unique in that they regulate not only the intensity and duration of the activities of cytokines that induce their production, but they also inhibit other related cytokines. With the aid of newly developed high sensitivity technology, investigators were able to show that Th1 and Th2 cells differ significantly in the sacs proteins that they produce. The parent cell from which Th1 and Th2 cells derive produces relatively low levels of SOCS proteins. However, its differentiation into either Th1 or Th2 cells is accompanied by dramatic changes in the levels and types of SOCS proteins it produces. Those cells that are destined to become Th2 cells produce levels of SOCS3 that are 23 times higher than the amount made by Th1 cells. In contrast, Th1 cells produce much higher amounts of SOCS1 than their Th2 "siblings".

Implications: These results suggest that mutually exclusive patterns of cytokine expression by Th1 and Th2 cells may derive in part from SOCS3- or SOCS1-mediated repression of requisite signaling pathways in Th2 and Th1 cells. SOCS1 and SOCS3 proteins are therefore T-cell lineage markers that can serve as therapeutic targets for immune modulation therapy. Drugs such as Remicade, Enbrel and Zenapax that inhibit cytokine activities are currently used to treat patients with uveitis, rheumatoid arthritis or other inflammatory disease. However, each of these drugs targets only a single cytokine. Because inflammatory diseases are characterized by production of copious amounts of a wide array of cytokines and SOCS proteins inhibit activities of multiple and diverse cytokines, therapeutic targeting of SOCS proteins would provide a more effective anti-inflammatory therapy.

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Benefits of Anti-HIV Therapy During Pregnancy Outweigh Risks

Background: Since 1994 most pregnant women infected with human immunodeficiency virus (HIV) have received some form of anti-HIV therapy to reduce its transmission to their newborns. HIV therapy involves treatment with inhibitors of an enzyme called reverse transcriptase, needed by the virus to copy itself; or with inhibitors of the enzyme protease, which allows HIV to infect cells. Anti-HIV therapy can be given using one reverse transcriptase inhibitor at a time (monotherapy), or using a combination of two or more reverse transcriptase inhibitors (combination therapy), or using a combination of reverse transcriptase inhibitors and protease inhibitors (combination therapy with protease inhibitors). The combination therapy with protease inhibitors has been shown to significantly reduce the likelihood of a mother passing the virus on to her child. However, recently a Swiss study showed that HIV-positive women who took the combination therapy with protease inhibitors were more likely to give birth prematurely than were HIV-positive women who did not take this therapy.

Advance: In response to the Swiss finding, researchers analyzed data from seven large studies that included a total of 3,266 pregnant women with HIV in the U.S. The researchers found no association between the use of combination therapy with protease inhibitors during pregnancy and an increased risk of birth complications, such as premature delivery, stillbirth, and low Apgar scores. (The Apgar test estimates a baby's general condition at birth, measuring characteristics such as heart rate, breathing, and muscle tone.) However, the researchers did observe a small association between this therapy and very low birth weight.

Implications: The data from this study should reassure physicians and HIV-infected women that antiretroviral therapies are not likely to increase the risk of many birth complications, and that the relatively low risks of using combination therapy with protease inhibitors are far more likely to be outweighed by the important benefit of preventing HIV transmission from mother to child. Further study is required, however, on the association between combination therapy with protease inhibitors and an increased risk of delivering a very low birth weight infant.

Tuomala RE, Shapiro DE, Mofenson LM, Bryson Y, Culnane M, Hughes MD, O'Sullivan MJ, Scott G, Stek AM, Wara D, Bulterys M: Antiretroviral therapy during pregnancy and the risk of an adverse outcome. N Engl J Med 346(24): 1863-1870, 2002.

Secretin is Not Effective in Treating the Symptoms of Autism

Background: Autism is a neurodevelopmental disorder characterized by social and communication problems and by repetitive behaviors and interests. There are no proven treatments for the social and communication deficits of autism, although it is often possible to treat some behavioral symptoms, such as aggression or hyperactivity. Secretin is a hormone that increases the flow of digestive fluids from the pancreas, and increases the production of bile in the liver and pepsin in the stomach. Secretin is also given routinely during some tests to diagnose intestinal ailments. Interest in secretin as a possible treatment for autism arose from reports that symptoms improved in autistic children who received a single dose of the synthetic form of human secretin during testing for other conditions. The children reportedly showed improved eye contact, alertness, and language skills. Subsequently, some physicians and caregivers started using secretin to treat symptoms of autism in children, although no experimental data established its effectiveness and safety. Given such concerns, researchers designed and conducted clinical studies. These showed that synthetic human secretin was no more useful than a placebo for treating the symptoms of autism. However, to rule out the possibility that a naturally-occurring form of the hormone might have a different effect than the synthetic version, researchers decided to test a form of natural secretin derived from pigs.

Advance: Fifty-six autistic children were randomized to receive either an intravenous dose of the natural form of secretin, followed by a dose of salt solution (used as a placebo) four weeks later, or to receive an intravenous dose of salt solution, followed by a dose of the secretin four weeks later. This "crossover design" allowed the researchers to evaluate the same children on both the experimental and placebo treatment. In essence, the children became their own controls, allowing researchers to assess if an individual child's unique combination of autistic-related behaviors and symptoms changed as a result of the therapy. To identify these changes, the children underwent detailed evaluations before treatment and follow-up testing every two weeks, over the following eight weeks. Researchers found no significant difference in the children when they received the natural secretin compared to when they received the saline solution. Results were the same eight weeks after the treatment was ended.

Implications: The current findings affirm that no form of the hormone secretin is effective for treating the symptoms of autism. However, the researchers caution that, because of the relatively small number of participating children, it is possible that a small subgroup of patients with autism may experience some benefit from secretin. Nonetheless, with the consistency of the findings over six studies, parents should no longer feel the need to refinance their homes or spend their life's savings to pay for this extremely expensive but ineffective treatment. This should help reassure parents that their children are not missing out on an important, life-changing, therapy.

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Engineering Technologies Improve Surgical Outcome in Patients With Epilepsy

Background: Epilepsy is a chronic medical condition produced by temporary changes in the electrical function of the brain. These changes can cause seizures that affect awareness, movement, or sensation. Severe seizures that resist treatment are associated with a shortened life span, risk of intellectual impairment and a sharply reduced quality of life. Seizures that cannot be controlled with drug therapy may be successfully treated with neurosurgical procedures. These procedures are designed to either remove brain regions that generate the seizures or to disconnect epileptic brain regions from other areas and prevent the spread of seizure activity. Advances in neuroimaging technologies have revolutionized the care of patients with certain forms of epilepsy and other neurologic disorders and are, in a large part, responsible for the recent enthusiasm for surgical treatment of these patients. Currently, the most useful imaging modalities used to evaluate individuals with epileptic seizures are magnetic resonance imaging and spectroscopy (MRI and MRS) and functional magnetic resonance imaging (fMRI). MRI and MRS provide a high-resolution image of the brain's internal structure while fMRI provides a picture of the brain's ever changing activity, rather than just its static structure.

Advance: Researchers funded by the NIH are developing new bioengineering strategies to study and treat neurologic disorders. These strategies capitalize on the combination and integration of advanced magnetic resonance technologies, allowing researchers to directly map changes in the brain that correspond to certain aspects of brain function. The goal of the project is to integrate information on the suspected location of the brain seizure with information about surrounding brain function in order to improve surgical outcome in epilepsy patients. Initial developments have already been applied to surgical procedures used to alleviate brain seizures in patients with epilepsy. In one case, an early form of surgery employing MRI strategies developed under this project was used to treat a patient suffering from as many as 100 seizures daily. Post-surgery, the patient’s seizures have almost completely stopped and the patient is experiencing a significant increase in quality of life.

Implications: The unique ability to directly observe brain function using a combination of MRI technologies provides new opportunities to advance our understanding of the brain’s organization as well as for studying and treating various aspects of neurologic disorders. In addition, technologies resulting from this study will lend much insight into the physiological properties of brain seizures in patients with epilepsy, substantially reduce the time required for complex neurosurgeries, and improve overall surgical outcome in patients.

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Antibiotic Treatment Controls the Vertigo of Ménière's Disease

Background: Ménière's disease is a distressing and often disabling disorder of inner ear function, characterized by spontaneous attacks of vertigo, fluctuating hearing loss, tinnitus and fullness in the ear. While there is currently no cure for the disease, its symptoms are often controlled by restricting the intake of salt and reducing the body's retention of fluid through dietary changes or medication. When vertigo cannot be controlled by diet or medication, surgery is another alternative. However, surgery sacrifices hearing and is used only for individuals with hearing loss in one ear. In addition, selective severing of a vestibular nerve from the affected ear usually controls vertigo while preserving hearing, but carries surgical risk. An alternative to surgery is injecting multiple doses of the antibiotic, gentamycin, through the eardrum, into the middle ear space (intratympanic injection) to deliver the drug to the inner ear. This treatment has gained popularity for controlling vertigo of Ménière's disease, however, its likely to cause high levels of sensorineural hearing loss. Recently, it was determined that a single transtympanic administration of gentamycin is effective in controlling vertigo in most individuals, without the risk of hearing loss associated with higher doses of aminoglycosides and surgical treatment.

Advance: NIH-supported scientists are currently investigating the effect of single-dose intratympanic gentamycin treatment on vestibular function in individuals with Ménière's disease in one ear. Clinical testing demonstrates that a single intratympanic gentamycin injection into the affected ear markedly reduces the vestibular response relative to pretreatment levels. Notably, the reduction of this response is not as severe as that seen after surgical treatment. Experimental studies suggest that gentamycin reduces vestibular responsiveness, and hence, vertigo, by causing a toxic effect on the vestibular hair cells, the sensory receptors that detect head motion stimuli and orientation. However, spontaneous activity is preserved in vestibular neurons after gentamycin administration, suggesting that vestibular hair cells are only partially damaged. While these hair cells can no longer respond to a vestibular sensory stimulus, they can still release neurotransmitters to the nerves.

Implications: This research demonstrates that a single intratympanic administration of gentamycin is effective at diminishing vestibular response and in controlling vertigo in individuals with Ménière's disease. Follow-up studies of these individuals demonstrate continued recovery of vestibular function over time following gentamycin treatment. Since there is no known cure for Ménière's disease, this finding provides a new treatment strategy that alleviates the disabling vertigo associated with the disease without significant impact to hearing or other risks of surgery.

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Carey JP, Minor LB, Peng GCY, Della Santina CC, Cremer PD, Haslwanter T: Changes in the Three-Dimensional Angular Vestibulo-Ocular Reflex Following Intratympanic Gentamycin for Ménière's Disease. Journal of the Association for Research in Otolaryngology 3(4): 430-443, 2002.

Novel Strategy to Treat Chronic Pain

Background: Chronic pain affects up to 50 million Americans each year, at an estimated social cost of $100 billion. Though current analgesic drugs, such as steroids, NSAIDs, opioids, and antidepressants, help many ease their discomfort, the pain management needs of millions of others remain completely or partially unmet. One source of the problem is nearly all available analgesics were developed based on overly simplified, linear models of pain transmission. Another is much of the pharmaceutical industry's investment in new analgesics aims either to optimize the chemical structure of existing agents or to better define known therapeutic targets. In both cases, the assumption is that a single "magic bullet" will control chronic pain. Recent advances in human biology, however, show that pain is a far more dynamic process that often involves multiple routes, or pathways. Each pathway integrates a convergence of molecular signals, then relays them along their own specific, hard-wired routes to the brain. This more complex model of pain transmission indicates that the most effective approach to relieve pain is to block, not one, but multiple routes of transmission at once. The research challenge is to define these routes in fine molecular detail, while also increasing the repertoire of pain management strategies to complement existing approaches.

Advance: NIH scientists have discovered a new approach to pain management that, based on their initial studies, selectively controls chronic pain associated with tissue damage and recurrent inflammatory processes of the skin, deep tissue, and joints. The discovery stems from laboratory studies of the cell-surface protein, vanilloid receptor I, known by the unrelated acronym TRPV1. The scientists knew prior to their studies that the TRPV1 receptor is expressed by a subset of pain-sensing neurons of the peripheral nervous system. They also knew that, once activated, TRPV1 likely opens a calcium-ion channel that ultimately produces sensations of heat, thermal pain, and inflammatory pain. What they discovered in cell culture experiments is they could use an ultrapotent compound with a known affinity for TRPV1 to overstimulate the calcium-ion channel, resulting in the death of the neuron. The group also observed that TRPV1 can integrate pain signals prompted by various molecules in the peripheral nervous system to produce sustained pain. They reached this conclusion by showing that a group of secreted, pro-inflammatory signaling molecules that are prevalent in the peripheral nervous system, called eicosanoids, likely bind to TRPV1 in a pH-dependent manner, similar to those found under pathological conditions.

Taken together, these observations suggested that an ultrapotent, TRPV1-binding compound could selectively eliminate an entire class of pain-sensing neurons from the peripheral nervous system of a living organism. In a recently published article, the group reported in animal studies that this turns out to be the case. The compound, called resiniferatoxin (RTX), killed the neurons, blocking inflammatory pain, hyperalgesia, and thermal pain sensation. Importantly, the animals maintained their ability to sense pain, in this case from a pinch, and they remained well

coordinated, an indication that RTX did not affect proprioceptive nerves in the muscles and joints.

Implications: These NIH researchers have yielded in just over a year of work a novel approach to pain management. This finding has important implications for the field of pain research, while it one day also could have broad implications on American public health. Additional studies are under way, with the ultimate goal of moving RTX or related compounds into human clinical trials.

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New Vaccine Target Identified for Oral and Other Cancers

Background: For most of the almost 1.3 million Americans who will be diagnosed this year with cancer, their treatment will involve chemotherapy, or the systemic administration of cancer-fighting drugs. Though chemotherapy benefits some patients, the vast majority of cancer-fighting drugs act non-specifically. These agents shrink tumors, but they also indiscriminately kill normal cells, producing unwanted and sometimes severe side effects. There is therefore a need to develop biologically sophisticated therapies that directly target tumor cells and leave normal cells untouched. One of the most promising approaches is immunotherapy, or training the body's immune system to recognize and attack cell-surface proteins specific to tumor cells. Most of the initial work on these so-called "cancer vaccines" has focused on melanoma. Some laboratories have begun to extend these investigations to oral cancer, including oral squamous cell carcinoma, the most common form of the disease. If successful, this research might one day provide a welcome alternative to disfiguring radiation and surgery, while also potentially improving the effectiveness of treatment.

Advance: A group of NIH-supported scientists recently identified six novel, tumor-specific antigens, or potential targets. Each of the antigens was derived from cyclin B1, a protein that helps to regulate the cell cycle. In their studies, the scientists exposed immune T cells in the laboratory to fellow immune cells that have the ability to present unique peptides, or bits of protein, on their surface. The idea was to determine if the T cells would attack as foreign individual peptides that had been extracted from an epithelial breast-cancer cell line, an indication that the immune system can be taught to remember and respond to the tumor antigen. The group found that the T cells mounted a vigorous response against six cyclin B1 peptides in particular.

Implications: This finding is particularly important because few tumor-specific targets have been identified in epithelial tumors, which cause over 80 percent of all cancers. To extend the finding, the group plans to launch small, early phase clinical trials involving people with oral squamous cell carcinoma, breast cancer, and lung cancer.

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Leptin – A Potential Treatment for Lipodystrophy

In 1994, scientists discovered the mouse obesity gene and its protein product, leptin. The discovery that this protein is secreted by fat cells and is released in proportion to the amount of fat drastically altered our view of normal adipose tissue as a passive "fat storehouse." Research fueled by this discovery has led to the identification of a number of substances that are secreted by fat cells and influence appetite and metabolism. Leptin, one such substance, is secreted into the bloodstream where it travels to the brain and signals the body to reduce food intake. Leptin also affects the liver, muscle, and pancreas – organs that influence the body's ability to use fats and sugar. In addition, leptin may affect one's food preferences and may lessen one's craving for "sweets." It can also suppress the activity of an enzyme necessary for fat production and improve insulin sensitivity in muscle and other tissues.

The fact that animals missing leptin were extremely obese and that the obesity could be reversed by administration of exogenous leptin led researchers to postulate that leptin treatment might be a successful therapy for human obesity. Indeed, very rare instances of complete deficiency of leptin in humans results in morbid obesity from infancy and these individuals suffer from a number of hormone abnormalities, including severe resistance to insulin – a hormone necessary to store and utilize food-derived glucose a key energy source necessary for daily life. Analogous to the treatment in mice, leptin treatment in these individuals caused substantial weight loss and improvement in the body's response to insulin providing hope for improved quality of life and longevity.

Unfortunately, leptin has not proven to be the "magic bullet" for the treatment of obesity in the vast majority of cases. Except in rare cases such as genetic mutations resulting in absence of leptin, obesity results from a complex interaction between our genes, our environment, particularly over-consumption and high fat foods, and our lifestyle. Obesity in general is characterized by very high levels of leptin which reflect the extent of obesity. The failure of the body to send signals to decrease food intake and increase expenditure of calories suggests that the more common forms of obesity are associated with a resistance to the actions of this hormone. Indeed, clinical trials in which leptin has been used to treat obese individuals so little or no effect of leptin treatment, even at concentrations much higher than would be seen normally.

Although leptin is not a successful treatment for weight loss in most cases of obesity, it has shown promise in treating other disorders. A particularly fascinating example is lipodystrophy. This is actually a group of disorders with disparate origins, some genetic and some acquired, but with a common set of characteristics. Individuals with lipodystrophy are characterized by lack of fatty tissue in the face, neck or extremities, sometimes with central obesity and sometimes lacking fat tissue altogether. These patients exhibit insulin resistance sometimes in the extreme and many have very low levels of leptin. Patients may have a range of lipid abnormalities and are at high risk to develop diabetes. Until recently, this group of diseases remained confounding

and difficult to treat. Treatment of lipodystrophy includes a combination of medications – insulin, oral hypoglycemic agents, and lipid-lowering drugs – to treat the metabolic abnormalities. In spite of treatment, patients continue to have severely high levels of triglycerides (hypertriglyceridemia), leading to recurrent attacks of acute inflammation of the pancreas; severe problems controlling blood sugar levels – posing risks of diabetic eye and kidney disease; and fat accumulation in the liver, which can result in cirrhosis and liver failure. Recent studies demonstrating a beneficial effect of leptin on insulin sensitivity and fat metabolism in a number of tissues along with the relative leptin deficiency seen in many patients with lipodystrophy suggest that leptin treatment might be effective in dealing with some aspects of this disease.

Two recent publications have reported exciting preliminary results of leptin treatment in individuals with lipodystrophy. One study treated individuals with congenital generalized lipodystrophy who also suffered from poorly controlled type 2 diabetes and hypertriglyceridemia. Following three to eight months of leptin treatment, all three patients showed marked improvement in insulin sensitivity, lower lipid levels, and decreased fat in the liver. At the time of the post-leptin treatment study, all patients were able to discontinue their diabetes medications. In addition, patients also reported a decrease in appetite and researchers observed an approximate 50 percent reduction in calorie intake. In concomitant animal studies using a lipodystrophy model, researchers demonstrated that leptin deficiency could explain most if not all of the confusing metabolic disturbances seen in this disorder.

Another recent clinical study tested the effect of leptin at approximately one-tenth of the dosage used for clinical studies of obesity in nine females with leptin deficiency and different forms of lipodystrophy. Eight of the nine individuals also had type 2 diabetes and were taking either insulin or a diabetes drug, or a combination of the two. During the four-month study, most of the women experienced significant improvements in levels of fasting glucose and in measures of their average blood glucose over the previous three months (hemoglobin A1c). These improvements in turn lowered their risk of developing diabetic eye and kidney complications. Triglyceride levels were also reduced – decreasing an individual's relative risk of developing cardiovascular disease. Liver size also decreased – indicating a loss of stored fat. Patients were able to reduce or stop using insulin and other drugs to control their diabetes, and they reported that they were eating less following treatment. Because of the dramatic improvement in their quality of life, all individuals in this study are continuing to receive leptin therapy.

Researchers recently identified the genes responsible for two forms of inherited lipodystrophy which should provide insight into both the heterogeneity of manifestations and the peculiar selectivity for fat depots in different regions of the body. Lipodystrophy can also be acquired and is often seen in individuals infected with the human immunodeficiency virus (HIV) who are undergoing treatment with highly active anti-retroviral therapy (HAART). Although HAART has dramatically improved the survival of people with HIV, it is associated with a variety of metabolic complications – including elevated fat levels in the blood, insulin resistance,

osteoporosis or bone loss, and lipodystrophy. Whether this metabolic syndrome is caused by this drug regimen or simply reflects unmasking of the effects of long-term infection due to increased survival is still under investigation. The earlier success with leptin in the treatment of lipodystrophy provides hope that it may be effective in HIV-associated lipodystrophy as well.

While lipodystrophy is characterized by loss of fatty tissue, in fact, these individuals still store fat. Many tissues including liver and muscle exhibit significant accumulation of fat within their cells and this abnormal fat deposition has deleterious effects on the metabolic activity of these tissues. Studies using mice have demonstrated that leptin is a critical hormone that helps muscle burn fat for energy rather than accumulating fat stores. Lipodystrophy is characterized by abnormal fat build-up in muscle and liver, a condition which was reversed in response to leptin therapy. Non-alcoholic steatohepatitis (NASH), a "silent" disease most common in adults over the age of 40 who are overweight, is another condition marked by inappropriate accumulation of fat, in this case in the liver. Individuals with NASH have insulin resistance, elevated levels of fats in their blood and are at high risk for the development of diabetes. Current approaches to treating NASH typically involve medications to improve the accompanying insulin resistance, as well as changes in diet and exercise to promote weight loss. While NASH and lipodystrophy share many features including intrahepatic fat build-up, NASH, like obesity, is correlated with high leptin levels. Thus, leptin resistance may well play a role in the development of this disease.

The discovery of leptin has led to a cascade of exciting and unexpected findings with broad implications for the successful treatment of disease. While the initial excitement was tempered by the lack of success in countering obesity, leptin is now proving efficacious as a therapy for a growing list of diseases and disorders including severe lipodystrophy. Researchers will continue to study individuals with less severe forms of lipodystrophy to determine if they too will benefit from leptin therapy. The promise that accompanied the discovery of leptin may yet be fulfilled. It is likely that future discoveries that do lead to effective tools to combat obesity will trace their origins to this remarkable discovery.

Progress in Understanding and Treating a Genetic Disease Affecting Reproduction and Fertility

Our ability to survive as a species as well as our ability to bear children and form families depends on our biological ability to reproduce. Human infertility is thus a source of great concern and psychological despair to the man and women that suffer from it and has been the subject of intense research in laboratories worldwide. Reproduction is controlled by a series of hormonal interactions that ensure both the development of the reproductive organs and the ongoing function of the reproductive system. Failure of any one of these complicated molecular processes can cause infertility and there are no simple ways to reverse this state. Hypogonadotropic hypogonadism (HH) is an example of a rare form of male infertility, caused by a genetic mutation. Hormones pass chemical signals from one organ or tissue in the body to another, causing changes in the cells of the target organ which in turn prepare it for new behaviors. In some forms of HH, one of these hormones, gonadotropin releasing hormone (GnRH), is unable to pass its signal to its target cells in the pituitary gland. The reason for this lack of communication is thus a key question.

Scientists from the Oregon Health Sciences University and their collaborators in Mexico have now discovered a way to reverse some of the defects that lead to HH. Patients with this disease were found to have defects not only in the hormone itself, but also in the pituitary cells with which the hormone communicates. Normally, the hormone latches on to or " docks" with a protein in target pituitary cells. This is the signal for these pituitary cells to release other hormones that will then "alert" the reproductive tissues. Such a docking protein is called a receptor and is normally in located on the surface of the cell where it can bind to hormone passing through the bloodstream. In patients with HH, the receptor is either not present on the cell surface or is not able to bind to the hormone. The gonadotropin releasing hormone (GnRH) receptor is a member of a large family of hormone receptors that affect many fundamental processes in humans and consequently cause many diseases when they are mutant. For this reason, pharmaceutical companies have intensively studied this family of proteins and have discovered many small chemicals that bind to these proteins and influence the way they bind to their hormones and transmit signals. The US Principal investigator in this collaboration was able to obtain a chemical from Merck that influenced the function of the normal GnRH receptor.

By adding this chemical to cells containing the defective receptor, researchers established the first clue that the defect could be reversed, the receptor could bind to its hormone almost normally and the signal could be passed on properly! Moreover, the same chemical could rescue all receptors from five different patients with HH, each of whom had defects that modified the shape of the protein in different ways. While these results have been obtained only in laboratory cells, there is good reason to suggest that similar effects may possibly be obtained in HH individuals with these defective genes, thus reversing the cause of their infertility.

These experiments not only offer hope for individuals suffering from hypogonadotrophic hypogonadism but also may offer a promising paradigm for treatment of other diseases. There is evidence Alzheimer's disease, Parkinson's, cystic fibrosis, nephrogenic diabetes insipidus, hypercholesterolemia, and retinitis pigmentosa all result from a mutant protein that has the wrong shape, causing it to end up in the wrong place in the cell and resulting in malfunction. If drugs similar to those used in the experiments with the GnRh receptor can be developed to bind with altered proteins and help them regain their normal shape and location on cell surface, this may prove to be a key research finding in the process of developing innovative drugs for these other disorders.

Individuals involved in many of these studies have been recipients of funding from the Fogarty International Center's research and training program in Population Health. It has resulted not only in numerous high quality publications, but has furthered training and capacity building in molecular expertise for the Mexican scientists who collaborated in the groundbreaking work. Most importantly the science of reproductive biology worldwide has been the beneficiary.

NIH-led Government and Private Venture Results in a New Medication for Opiate Addiction that Can be Prescribed in Doctor's Offices

The number of individuals suffering from heroin and other opiate addictions is about to be reduced thanks in large part to a public/private research undertaking that has resulted in a new medication. The separate passage of legislation allowing this new drug to be prescribed in physicians' offices will further help reduce the treatment gap, or the number of persons who need, but do not receive, treatment for drug abuse or addiction.

This new medication, known as buprenorphine, offers a valuable tool for physicians to use in treating the nearly 900,000 chronic heroin users in this country. It will also be useful for treating the growing number of individuals who misuse and become addicted to prescription pain-killers. The story of how buprenorphine came to fruition exemplifies how long-term investments in research can result in tangible products that dramatically impact the health of the public.

Subutex (buprenorphine) and Suboxone (buprenorphine with naloxone) tablets were approved by the Food and Drug Administration (FDA) on October 8, 2002. This approval came after the products were studied in over 2000 patients and found to be safe and effective treatments for opiate addiction. These are the first drugs available for the treatment of opiate addiction that can be prescribed in an office setting, like medications commonly used to treat diabetes or hypertension. Other medications for addiction, such as methadone, can only be dispensed through federally licensed addiction treatment clinics. The "Drug Addiction Treatment Act of 2000", [Title XXXV of P.L. 106-310] amends a provision of the Controlled Substances Act (21USC 823 (g)) to enable qualified physicians to prescribe and dispense buprenorphine medications to patients at the doctor's office, rather than at a clinic.

In addition to an act of Congress, it also took an investment of many years and resources from NIH's National Institute on Drug Abuse (NIDA), its partnering pharmaceutical company, and others, to develop a medication that would be safe, effective and well tolerated by patients. It is buprenorphine's pharmacology that makes it an attractive, clinically relevant, treatment option. Both Subutex and Suboxone contain the active ingredient buprenorphine, a partial agonist that functions on the same brain receptors as morphine, but does not produce the same high, dependence, or withdrawal syndrome. Buprenorphine actually prevents morphine from binding to opiate receptors, thus blocking its pleasurable effects. Buprenorphine also blocks withdrawal discomfort by keeping the receptors occupied. It is long-lasting, less likely to cause respiratory depression, well tolerated by addicts and, when combined with naloxone, has very limited diversion potential.

Buprenorphine was first synthesized in 1969 in England by Dr. John Lewis of Reckitt and Colman Products and subsequently developed as an analgesic. It was initially marketed in the United Kingdom in 1978 for injection and in 1981 and 1982 as a sublingual tablet. It is being

marketed today in over 40 countries as an analgesic. It has been used in the US since 1985, but only in its injectable form.

In the mid 1970s researchers at the Addiction Research Center in Lexington, KY (NIDA's intramural research program at that time) began to take an interest in buprenorphine as a medication that might work for treating opiate addiction. In 1978 Dr. Donald Jasinski and colleagues, in a landmark clinical study, showed that buprenorphine can in fact block the euphoria produced by other opiate drugs (Archives of General Psychiatry 35:501-516). Other researchers were also reporting that daily administration of buprenorphine decreased heroin self-administration in opiate abusers. Numerous studies on buprenorphine continued throughout the 1980s and 1990s.

Congress, recognizing the need to stimulate the availability of addiction medications, passed several pieces of precursor legislation during the 1970s and 1980s indicating its intention that NIDA initiate and promote research into the creation, development and testing of pharmacological substances for treatment of addiction. NIDA administratively created a Medications Development Division to focus on this effort in 1990. In 1992, Congress passed the "ADAMHA Reorganization Act" (P.L. 102-321), which statutorily established the Medications Development Program at NIDA.

By then the NIDA medications program supported a number of major studies that documented buprenorphine's safety and efficacy in the opiate-abusing population. With the bulk of the research completed, NIDA established a Cooperative Research and Development Agreement in 1994 with the original developers of the medication, Reckitt and Colman Pharmaceuticals, Inc (now Reckitt Benckiser). This was a team effort to bring the drug to a marketable status for treatment of opiate addiction in the United States. In 1999, Reckitt submitted all of the study data to the FDA in support of a new drug application (NDA) for buprenorphine in the treatment of opiate dependence. The FDA found the 2mg and 8 mg tablets to be safe and effective and gave final approval in October 2002.

For the first time, the disease of addiction will be put on an equal footing with other chronic diseases. Buprenorphine and buprenorphine/naloxone products are expected to increase the amount of treatment capacity available and expand the range of treatment options and settings that can be used by physicians. Because NIH worked with a sister agency, the Substance Abuse and Mental Health Services Administration (SAMHSA), while developing the medication, approximately 2000 physicians have already received the necessary training to offer this new treatment option to their patients. This long-term collaborative venture, undertaken by components of the federal government (Department of Health and Human Services: NIH/NIDA, SAMHSA, and FDA, and the Department of Justice: Drug Enforcement Administration) and by the private sector (Reckitt Benckiser Pharmaceuticals), showcases the new multidisciplinary pathway that discovery can take to truly impact the health of the public.

Drug Addiction, Stress, and New Targets for Treatment

Exposure to stress is an all-too-frequent occurrence in today's world, and can also be one of the most powerful triggers of substance abuse in vulnerable individuals and of relapse in former addicts. Recently, scientists have begun to unravel some of the neurobiological mechanisms of this complex relationship. With this knowledge, we are now in a position to target treatment approaches to the specific brain pathways that mediate substance abuse and the effects of stress.

Stress influences a variety of physiological and immunological responses. Although acute stress can be life saving, chronic stress can lead to a variety of physical and mental ailments, including substance abuse. Interestingly, exposure to or withdrawal from drugs of abuse can also perturb an individual's stress response systems which can further increase vulnerability to drug usage. In this manner, stress can lead to a self-perpetuating cycle of accelerating drug abuse.

Evidence for the intimate relationship between stress and drug use began to emerge in the 1980s, when it was discovered that even mild stress could increase animals' behavioral response to and self-administration of drugs of abuse. More recently, scientists have found that individual differences in levels of stress hormones could predict the nature of the behavioral effects of several drugs of abuse. In addition, individual differences in reactivity to stress have been found to differentially affect vulnerability to drug taking.

One of the hallmarks of drug addiction is the propensity to relapse to drug use even after extended periods of abstinence. Animal models of relapse have helped increase our understanding of the factors that can lead to relapse, and again, stress has been found to be of great importance. For example, in one series of experiments, rats were allowed to self-administer drugs by a simple voluntary response such as pressing a lever. Exposure to these sorts of circumstances readily leads to drug taking and the development of drug dependence in the rats. Once these drug-taking behaviors become established, access to the drug can be discontinued by replacing the drug solution with saline. As the animal learns that drug is no longer available, the behavior that previously produced drug infusions diminishes or ceases completely. The question may then be asked as to what conditions might reinstate an animal's attempts to self-administer drugs, even after weeks of drug unavailability. Several events have been found capable of re-triggering drug-seeking or relapse in this model. Among these are: re-exposure to even a small amount of the drug; exposure to cues previously paired with drug use; and exposure to virtually any stressor.

Animal models such as these are proving to be valuable to evaluate medications and behavioral manipulations that can prevent relapse. For example, compounds recently developed to block the initiation of the stress hormone cascade (corticotropin-releasing factor receptor antagonists, or simply CRF antagonists) have shown a remarkable ability to block stress-induced reinstatement of drug-seeking for a number of drugs of abuse, including cocaine, amphetamine, heroin, and alcohol. Furthermore, other studies have found CRF antagonists are effective in

blocking both the initiation and maintenance of drug taking in animals. Evaluation of these medications in clinical trials for anxiety and depression is ongoing. This work will facilitate assessment of these compounds in the treatment of human drug abuse as well.

In the wake of the tragic events of September 11th, awareness of the role that stress can play in increasing vulnerability to drug use is more important than ever. People continue to struggle with the emotional impact of those terrorist acts, and with the uncertainty of what may lie ahead. Increased drug and alcohol use by people close to the World Trade Center attack has been found by researchers, particularly in individuals with stress-related and depressive disorders. Research has provided us with a better understanding of the relationship of stress to substance abuse and mental disorders. This has in turn led to a growing recognition that stress-related treatment efforts following traumatic events need to consider substance abuse as part of their overall goal of restoring the health and well-being of those affected. Likewise, treatment programs for substance abuse must also target stress-related factors to maximize chances for long-term recovery. We can extend this knowledge through clinical trials of the new CRF receptor antagonists for the treatment of drug abuse. In the past, those individuals with co-occurring substance use, anxiety, and depressive disorders faced a poor prognosis for recovery. Research discoveries now offer new hope for improved treatment by means never before possible.

New Treatments for Diabetic Retinopathy and Age-Related Macular Degeneration

The formation of new blood vessels, or angiogenesis, within the eye is a fundamental process which occurs not only in normal development but also in a wide range of eye diseases. In normal human adults, angiogenesis occurs when new vessels grow from pre-existing ones. This is a highly regulated process limited to wound healing, pregnancy, and cyclic uterine physiology. Under abnormal conditions such as cancer, the growth of new host blood vessels into the tumor results from a response to tumor-derived factors.

Proliferation of new blood vessels, or neovascularization, also occurs as the dominant feature in many blinding eye diseases: proliferative diabetic retinopathy(PDR), age-related macular degeneration (AMD), certain kinds of glaucoma, and retinopathy of prematurity (ROP). The leading cause of vision loss for Americans under the age of 65 is diabetes. Sixteen million persons in the United States are diabetic and 40,000 new patients each year suffer from ocular complications of the disease. Pathological growth of new vessels in the retina or choroid lead to visual loss in diabetic retinopathy (DR) and AMD, respectively. While inhibition of abnormal new vessel growth would not necessarily cure the underlying disease, it would preserve vision by preventing complications associated with neovascularization, such as hemorrhage and edema.

The potential role of growth factors as mediators of developmental and pathological intraocular vascularization has been recognized for almost half a century. The molecular understanding of events involved in the process of angiogenesis has advanced significantly since the purification of the first angiogenic molecules nearly two decades ago. But it wasn't until 1980 that an aqueous extract of retinas from freshly enucleated mammalian eyes was shown to liberate a vascular cell proliferative factor, later identified as basic fibroblast growth factor (bFGF). Then, in the mid 1990s investigators discovered that a specific molecule, vascular endothelial growth factor or VEGF, appeared to have angiogenic and vasopermeability activity. Although originally studied for its role in tumor development, it received considerable attention, because it seemed to account for the association between neovascular disease of the retina and increased vasopermeability. Patients with diabetic retinopathy showed a clear correlation between the extent of their disease and the levels of VEGF in their eye. It appeared logical that a fine balance must exist between molecules that can switch on the process of new vessel growth and those that inhibit it. Indeed, over the past decade researchers have discovered that angiogenesis can be turned on by molecules like basic and acidic FGF, VEGF, transforming growth factor, interferon, tumor necrosis factor-alpha, and platelet-derived growth factor. On the other hand, angiogenesis is suppressed by inhibitory molecules such as thrombospondin-1, angiostatin, endostatin, PEX, and pigment epithelial derived factor (PEDF). When the balance between stimulation and inhibition of blood vessel growth is upset, as in certain diseases, capillary cells are induced to proliferate, migrate, and ultimately differentiate into vessels.

As interest in ocular angiogenesis increased in the 1990s, vision researchers identified new molecules involved in ocular angiogenesis. VEGF was discovered to be linked to a cellular

metabolic pathway involving the signaling molecule phosphoinositol. Inhibitors of this pathway called protein kinase C inhibitors as well as inhibitors of the specific molecule that is inhibited were developed. Compounds called integrins were shown to be specifically associated with proliferating vascular endothelial cells in cases of PDR. Studies in animals demonstrated that angiogenesis could be blocked with an integrin inhibitor. These discoveries helped fuel suggestions that therapies for abnormal retinal angiogenesis could be developed to prevent people going blind from vascular proliferative diseases. Clinical trials began to test the efficacy of protein kinase C and somatostatin inhibitors in preventing the progression of diabetic retinopathy. Similarly, VEGF aptamers (which are strands of DNA or RNA molecules that bind to specific molecular targets) and antibodies, protein kinase C antagonists, and angiostatic steroids are currently in clinical trials for neovascular AMD.

A recent exciting finding has been the observation that a molecule involved in protein synthesis is also anti-angiogenic. Protein synthesis involves specific carrier molecules, tRNA, which bind single amino acids that will potentially be incorporated into a protein. An enzyme called a synthetase participates in this binding. Synthetases are named for the amino acid whose incorporation they facilitate. One such specific enzyme, the tryptophanyl-tRNA synthetase (TrpRS) appears to have another function in the cell. TrpRS is also involved in cell signaling so that information from outside the cell can be transmitted inside the cell. TrpRS is synthesized in two forms, one that incorporates tryptophan into protein and a shorter form called mini TrpRS. Only the longer, full length enzyme functions by adding tryptophan to protein; mini TrpRS is catalytically inactive for protein synthesis. The mini-synthetase is found in small amounts but was found to have anti-angiogenic activity. Indeed, mini TrpRS inhibits growth and migration of blood vessel cells that were exposed to agents that induce angiogenesis, such as VEGF, the molecule identified in patients with proliferative diabetic retinopathy. In addition, mini TrpRS may also inhibit the growth of new blood vessels in animal eyes and tumors.

Recently, adult bone marrow-derived stem cells have been found to seek out and become incorporated into newly forming blood vessels of the retina. Such selective targeting is of great significance when designing human therapeutic approaches. Adult human bone marrow contains two classes of cells, those which are hematopoietic (can form blood cells) and those which are not. The population of stems cells that does not play a role in blood formation contains endothelial precursors cells (EPCs) that can form blood vessels. When the EPCs are injected into neonatal mouse eyes, they extensively and stably incorporate into forming retinal vasculature. Further, when injected into a mouse with a retinal degeneration whose vasculature normally degenerates with age, they rescue and maintain a normal vasculature. For therapeutic purposes it would be ideal if these specialized EPCs could be packaged with an inhibitor and then delivered to compromised vasculature for rescue. Such a possibility was demonstrated by an experiment in which mini TrpRS was incorporated into EPCs and inhibited normal mouse blood vessel development. This exciting result indicates the possibility that local delivery of pharmacological agents in physiological meaningful doses may represent a new method for treating neovascular diseases of the eye.